The potential for vaginal self sampling to increase participation in cervical screening

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To my wife, Nirmalie, two sons, Kethmin and Kevin and everyone who has helped me to learn…..

STATEMENT OF ORIGINALITY

I, Lilantha Wedisinghe, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

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ABSTRACT

Aim: To explore potential methods of increasing cervical screening coverage.

Methods: Cervical screening defaulters in Dumfries and Galloway were identified in 2012, split into a control (N=64) and 7 intervention groups who were offered multiple screening options including self-collecting a vaginal sample at home. Self-samples were tested for high-risk human papillomavirus (HPV). A total of 3323 were invited to request a kit and 492 were sent a kit directly. Women who declined screening were asked to complete a questionnaire. Colposcopy referrals from defaulters were audited to identify changes over time. Defaulters attending the hospital smear clinic were questioned to ascertain barriers to cervical screening.

Results: Among seven intervention groups the proportion responding varied between 32% (25%-38%) and 14% (11%-17%) compared to 6% among controls. One hundred and thirty women were HPV positive on self-sample, 8 of whom had CIN2+ diagnosed. A significantly higher number of defaulters were referred to colposcopy in June-December 2012 (n=51) than in the same period in 2011 (n=17; OR=3.8, 2.1-6.9). Defaulting was more commonly attributed to practical (112/155=72%) than attitudinal barriers (23/115=15%) (RR=4.9, 3.3-8.0).

Conclusions: Practical barriers are often the cause of women not attending for cervical screening and offering more options, particularly the option of self-sampling at home, increases screening coverage.

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LIST OF ABBREVIATIONS

AGC - abnormal glandular cells
ASCUS- abnormal squamous cells of unknown significance
CGIN - cervical glandular intraepithelial neoplasia
CIN - cervical intraepithelial neoplasia
DNA - deoxyribose nucleic acid
FTA - Flinders Technology Associates
gDNA - genomic deoxyribose nucleic acid
mRNA - messenger ribonucleic acid
HC2 - hybrid capture 2
HG - high grade
HPV - human papillomavirus
HR - high risk
HSIL - high-grade squamous intra-epithelial lesion
HTA - high throughput assay
LBC - liquid based cytology
LG - low grade
LiPA - line probe assay
LLETZ- large loop excision of transformation zone
LR - low risk
LSIL - low-grade squamous intra-epithelial lesion
NA - not available
NPV - negative predictive value
PI - principal investigator
PPV - positive predictive value
RNA - ribonucleic acid
SCCRS- Scottish cervical call-recall system
TOC - test of cure

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Dr Jo Waller kindly gave the permission to use the questions of the questionnaires that were used to collect qualitative data for her research. She also reviewed the website and advised on its content. I thank Ms Jacqui Hutchison and Ms Polly Rawlinson for proof reading.

DETAILS OF COLLABORATION

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Other investigators: Professor Heather Cubie (Scottish HPV Reference Centre, Edinburgh). Dr Maurice Canham (Scottish HPV Reference Centre, Edinburgh). Mr Allan Wilson, Lead Biomedical Scientist, Regional Cytology Centre, Monklands).

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CHAPTER 1

Introduction and literature review

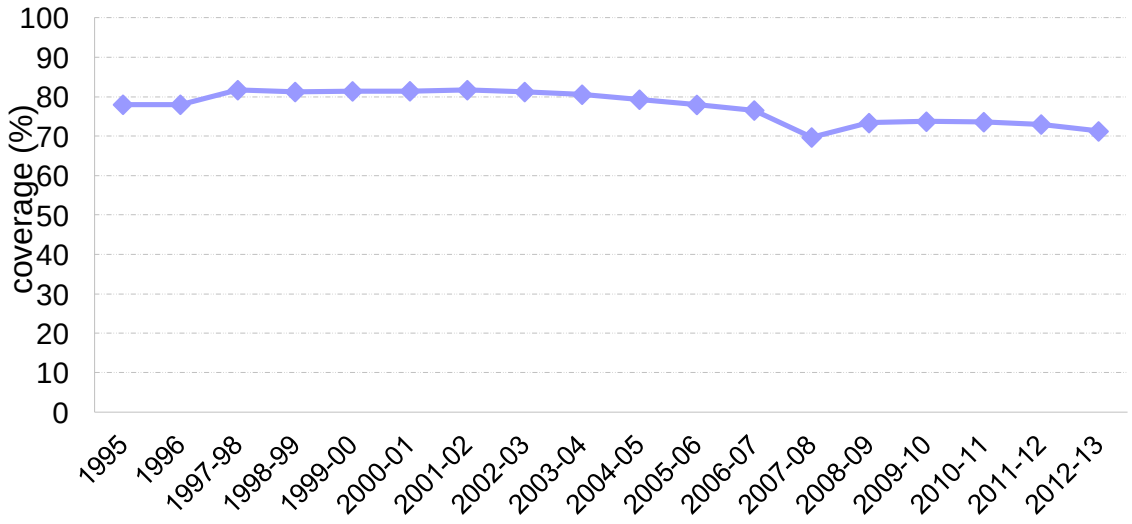
1.1. INTRODUCTION

Cervical cancer prevention

Each year in the UK about 2800 women are diagnosed with cervical cancer and 1000 die from the disease (Aapro, Fabi et al. 2010; NHSCSP 2011). Most women who develop cancer have not been screened regularly. According to a national audit in England (NHSCSP 2011), the majority (1345/1896=71%) of cervical cancer cases diagnosed in younger (<50 year old) women were those who hadn't had a screening test in the previous three and a half years. The three and a half yearly screening coverage in the 25-49 year group in England had been between 69% and 74% during this period (NHSCSP 2012). National audit reports from other countries also revealed that most women who developed cervical cancer were overdue for screening (Bergstrom, Sparen et al. 1999; Bos, Rebolj et al. 2006; Andrae, Kemetli et al. 2008). In high-income countries, more than half of the women who were diagnosed with cervical cancer had never had a Pap test or were infrequently screened (van der Graaf, Zielhuis et al. 1988; National Institutes of Health 1996; Sasieni, Cuzick et al. 1996; Bekkers, Massuger et al. 2004; Bekkers, Meijer et al. 2006; Ingemann-Hansen, Lidang et al. 2008).

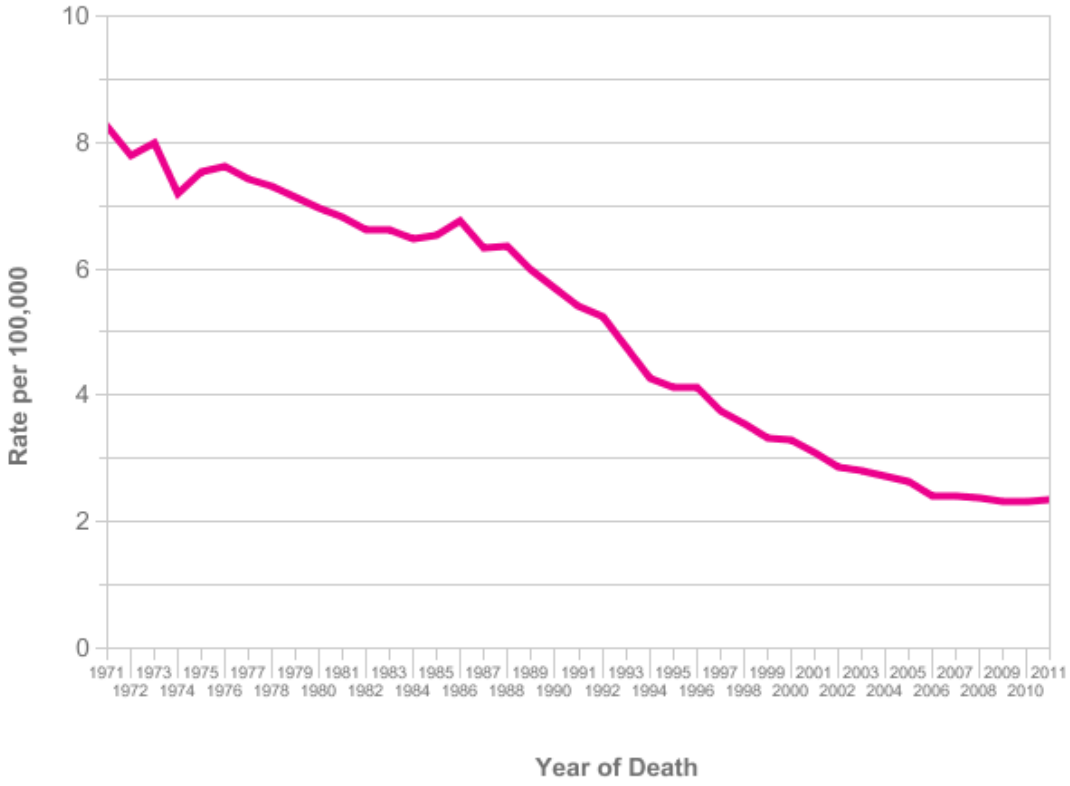
Although routine cervical screening represents an effective tool in the early detection of cervical cancer, it remains underused by some women. A declining trend seen in the Scottish cervical smear uptake rate from 81% in 2003 to 71% in 2013 (ISD Scotland 2013), appears alarming.

Fig 1.1.1 Trends seen in Scotland's cervical screening coverage (ISD Scotland 2013)



More worryingly, the cervical cancer mortality rate in the UK has remained static at around 1000 per year since 2006 (Fig 1.1.2). These trends are unlikely to improve unless different strategies are adopted (Giorgi Rossi, Marsili et al. 2011).

Fig 1.1.2 Cervical cancer mortality rate in UK (per 100,000) (CRUK 2014)

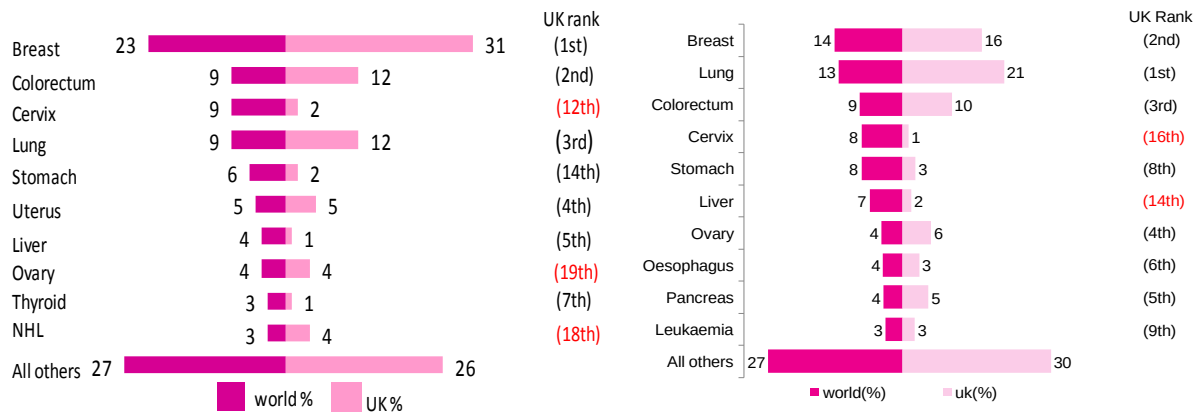


Cervical cancer is potentially one of the most preventable cancers (IARC 2005). The benefits of cervical screening are conferred on those who are actually screened. Despite the known value of cervical screening, a significant number of women do not avail themselves of the procedure (Anttila, Ronco et al. 2004).

Potential ways of reducing cervical cancer mortality

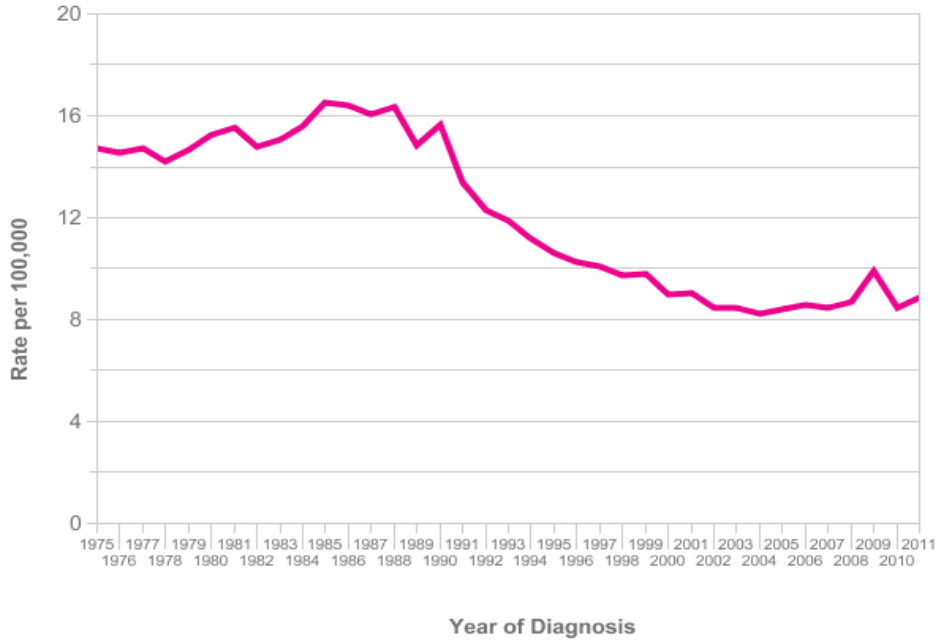
Whilst cervical cancer is the third most common cancer diagnosed in women in the world, it is ranked number 12 in the UK (Fig 1.1.3.a). Although cervical cancer is the fourth most common cause of cancer deaths in women in the world, it is ranked number 16 in the UK (Fig 1.1.3.b).

Fig 1.1.3: (a) The ten most commonly diagnosed cancers (b) The ten most common cancer deaths in females worldwide 2008 [with comparison to UK 2008] (Cancer Research UK 1 2013)



This mortality difference is mainly due to the rapid decline in the incidence of cervical cancer seen over the past 3 decades. However, the cervical cancer mortality rate in the UK remained static around 1000 deaths per year from 2006 to 2011 (Fig 1.1.2). A similar trend is seen in the incidence of cervical cancer over a decade (Fig 1.1.4). Hopefully, the HPV vaccination which began in 2008 will ameliorate this situation in the future.

Fig 1.1.4: European age-standardised incidence rates per 100,000 population, females, Great Britain. (Cancer Research UK 2014)



Although relatively low numbers of new cervical cancer cases (802/3107=26%) are diagnosed after the age of 60 years (Fig 1.1.5 and Table 1.1.1), the majority of deaths (545/956=57%) occurred in this age group (Fig 1.1.6 and Table 1.1.1). The high mortality to incidence ratio 68% (545/802) reflects the poor prognosis owing to the advanced stage at disease presentation. Cervical screening currently stops at the age of 58-64 in the UK.

Fig 1.1.5: Average number of new cases per year [and age-specific incidence rates per 100,000 population, females, UK] (Cancer Research UK 2014)

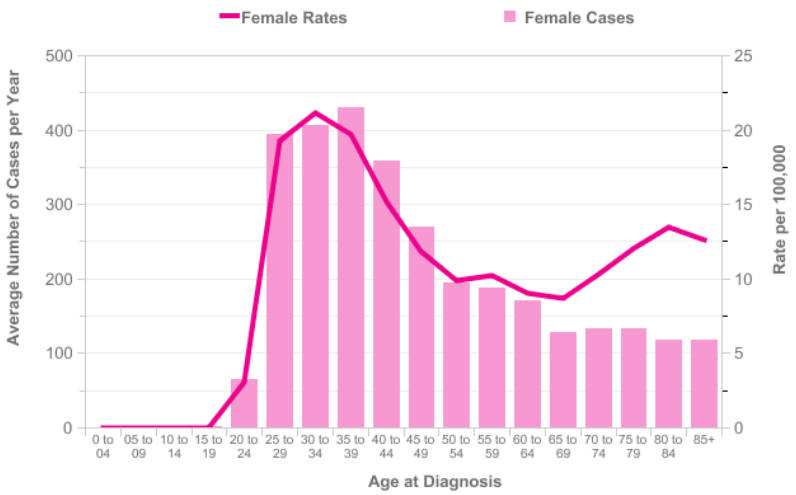


Fig 1.1.6: Average number of deaths per year [and age-specific mortality rates per 100,000 population, females, UK] (Cancer Research UK 2014)

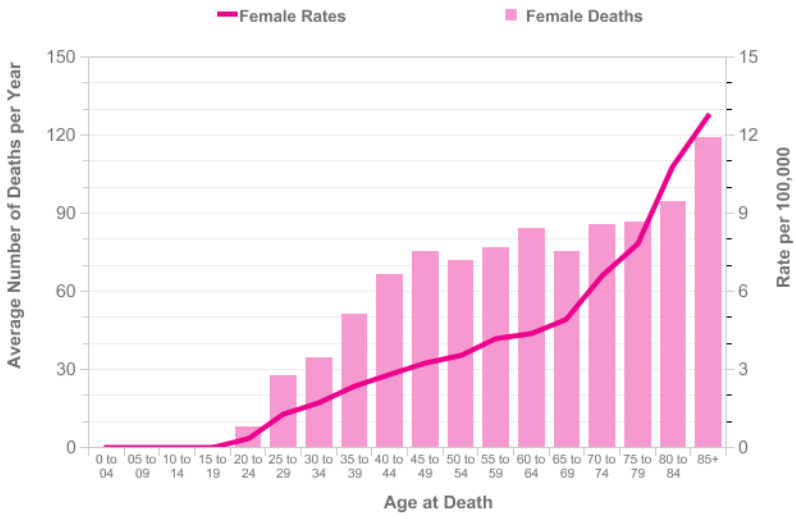


Table 1.1.1: Average number of new cases per year [and age-specific incidence rates per 100,000 population, females, UK] and average number of deaths* per year [and age-specific mortality rates** per 100,000 population, females, UK] (Cancer Research UK 1 2013)

Age Range	Cases	Incidence rate	Deaths*	Mortality rate**
0 to 04	0	0	0	0
05 to 09	0	0	0	0
10 to 14	0	0	0	0
15 to 19	1	0	0	0
20 to 24	65	3.1	8	0.4
25 to 29	395	19.3	27	1.3
30 to 34	406	21.2	35	1.7
35 to 39	429	19.7	51	2.4
40 to 44	359	15.2	66	2.8
45 to 49	269	11.9	75	3.2
50 to 54	194	9.9	72	3.5
55 to 59	187	10.2	77	4.2
60 to 64	171	9	84	4.4
65 to 69	128	8.7	75	4.9
70 to 74	133	10.3	86	6.6
75 to 79	134	12	86	7.8
80 to 84	118	13.5	95	10.8
85+	118	12.6	119	12.7
All Ages	3,107	9.9	956	3

About half of cervical cancer deaths in the recent past in the UK occurred after the screening has stopped. It is very unlikely that women after the age of 60 years have acquired new HPV infections. However, virtually all of these cancers were caused by persistent HPV infection. Therefore, it seems vital to recognise women with persistent cervical/genital HPV infection, before women 'retire' from cervical screening, in order to reduce this high number of cervical cancer deaths in the elderly.

Barriers to get screened

Evidence suggests that practical issues such as difficulty gaining access to a female smear taker, communication barriers, inaccessible locations, unfavourable appointment times, physical disability, previous bad experience, work and family commitments affected women's decision making more than attitudinal barriers (Waller, Bartoszek et al. 2009). Offering more flexible and convenient cervical screening options such as self-collection for *Human Papillomavirus* (HPV) testing might increase the screening coverage (Bais, van Kemenade et al. 2007; Giorgi Rossi, Marsili et al. 2011; Virtanen, Anttila et al. 2011).

Anatomy of the cervix

The uterine cervix is also called the neck of the womb. It is the part of the female genitalia between the uterine body (corpus) and the vagina (Fig 1.1.7). Cylindrical in shape, the cervix consists of two major parts: the ectocervix and the endocervix. The ectocervix is dome shape when seen through the vagina. The endocervix is the middle canal-like portion which opens into the uterus though the internal os. The size, shape and the colour of the cervix depend on a woman's age, hormonal state and whether or not she has given birth. A non-pregnant cervix is smooth, firm in consistency, pink in colour, cylindrical in shape and measures approximately 2-3cm in diameter and 3-4cm in length.

Fig 1.1.7: Female reproductive organs

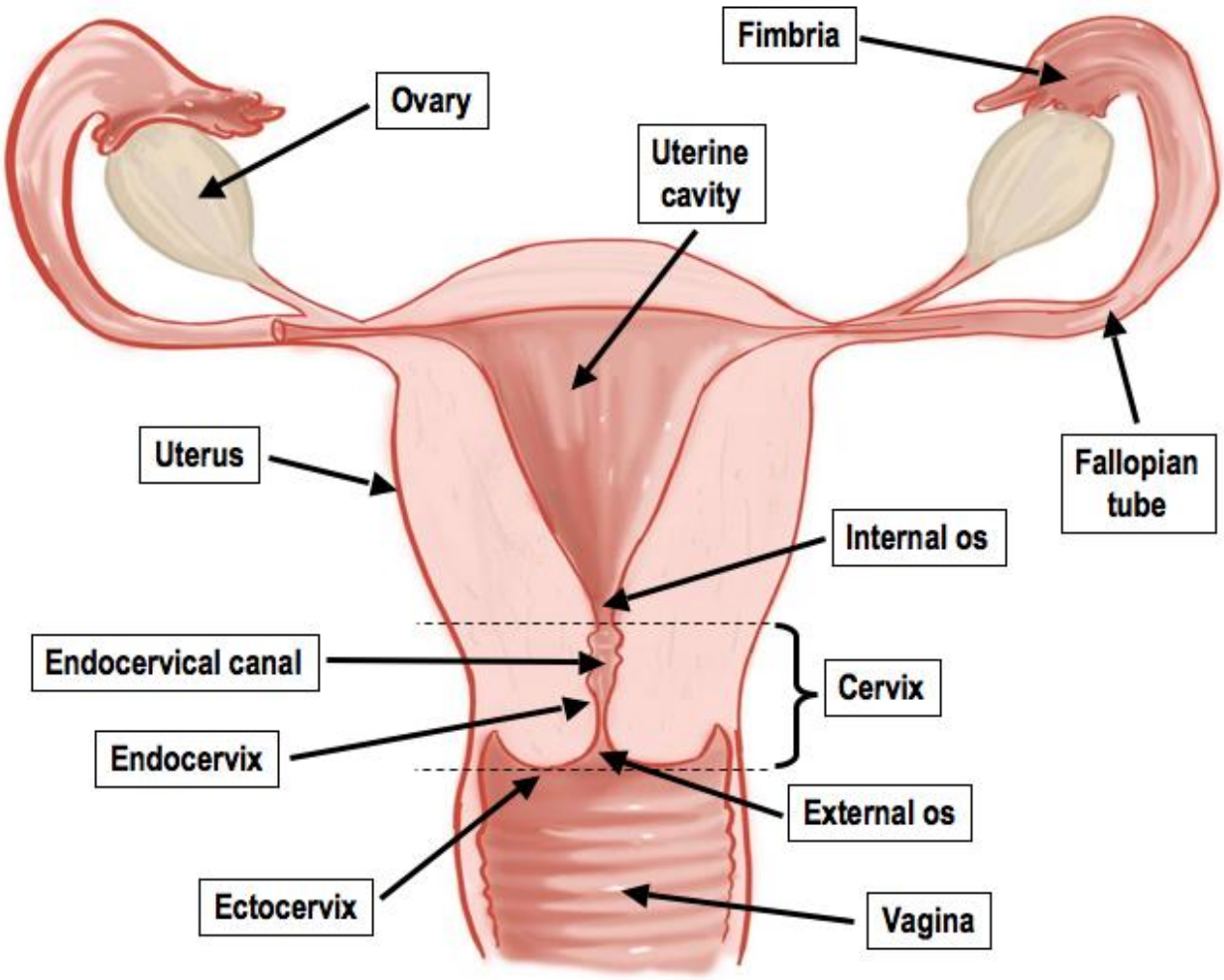


Figure courtesy of Dellaesque Photography, London

Cervical neoplasia

Cancer affecting the cervix is one of the most common female cancers. It is the second most common female cancer in women in developing countries (International Agency for Research on Cancer (IARC) 2004). Cervical cancer is estimated to cause one death every two minutes worldwide. Virtually all (>99%) cervical cancer is caused by the persistent Human Papillomavirus (HPV) infection (Walboomers, Jacobs et al. 1999; Cogliano, Baan et al. 2005). The viral oncogenic process is well understood (zur Hausen 1991; Bosch, Manos et al. 1995). Whilst most cervical cancers are squamous carcinomas, about 20% are adenocarcinomas (NHSCSP 2011). Whilst squamous carcinomas are known to originate from the squamous epithelium which is the lining of the ectocervix, adenocarcinomas originate from the columnar epithelium, which is the lining of the endocervical canal.

Fig 1.1.8: Cervical squamo-columnar junction and transformation zone

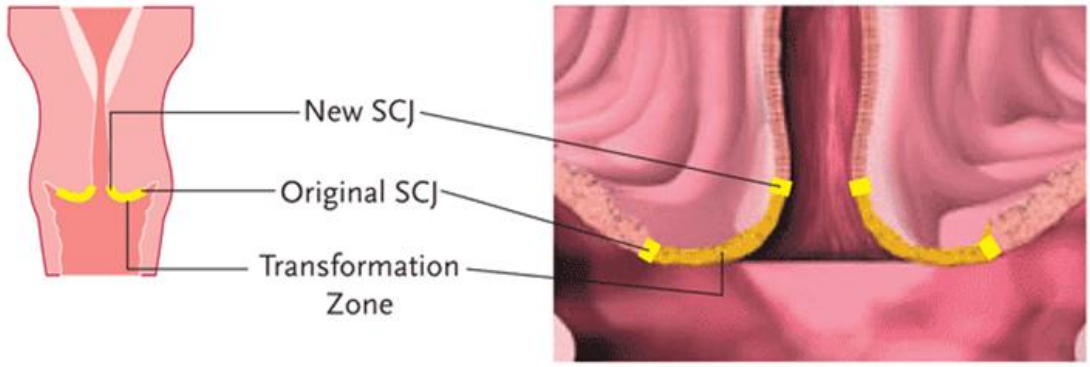


Figure courtesy of Merck & Co., Inc.

Hallmark of screening

The anatomical junction between the endocervical columnar epithelium and the ectocervical squamous epithelium is called the squamo-columnar junction (SCJ, Fig 1.1.8), where these two epithelia merge. Anatomical location of the SCJ on the cervix changes over the course of reproductive life of a woman, as the cervix has to adapt to various unique functions such as acting as the gateway for the sperm to enter the womb and acting as a barrier to microorganisms. The zone between the original SCJ and the new SCJ is called the transformation zone (TZ). Cells of the new SCJ are most susceptible for HPV induced neoplasia (cancer and pre-cancer). The transformation zone is the most vulnerable area of the cervix for developing cervical cancer. Therefore, colposcopy examination of the SCJ and the TZ remains the mainstay of making a clinical diagnosis of cervical neoplasia. This allows the colposcopist to

obtain directed biopsies from target lesions which enable the making of a definitive histological diagnosis. Similarly, proper sampling of SCJ and the TZ is essential for a cervical smear (cytology) test, but it is not essential when screening for HPV infection alone. However, isolation of HPV in a cervical sample would be a better surrogate marker of disease presence. If HPV screen positive women were to go through a secondary screening test (e.g. cervical cytology) prior to the diagnostic test (colposcopy), then proper cervical sampling would become a less important requirement in HPV screening.

Conventional Pap smear screening

A conventional method of cervical screening is the Pap smear test. Obtaining cervical scrapes with a wooden spatula to make a smear of cells on a glass slide to be examined under a light microscope after staining was the basis of the conventional Pap smear test. Sensitivity of recognising hgCIN of the Pap smear test varies, but is generally about 50%. The sensitivity of the Pap test of 55.4% (95% CI= 33.6-77.2; P=0.01) was significantly lower than the sensitivity of the HPV test of 94.6% (95% CI= 84.2 -100)) in a randomised controlled study involving over 10,000 participants (Mayrand, Duarte-Franco et al. 2007) when a result of ASCUS, AGC or worse was considered positive to detect CIN2+. However, the sensitivity of the Pap test depends on the quality of the test which involves several steps, sampling, processing and interpretation. A recent study reported that the relative sensitivity of HPV testing was 3.4 times greater (2.4-4.9) than the conventional Pap smear for detecting hgCIN (Lazcano-Ponce, Lorincz et al. 2011). Poor quality Pap smears could confound this higher relative sensitivity ratio.

Liquid based cytology (LBC) screening

In the UK, the conventional Pap smear was replaced by liquid based cytology which seemingly has a higher sensitivity (60-65%) for detecting hgCIN, although this has never been shown in a controlled trial. LBC had reduced the unsatisfactory test results to 2-3% (Health and Social Care Information Centre 2013). The fundamental difference between the conventional Pap smear test and LBC is the suspension of the cytology sample in a liquid preservative medium and making a thin film of cells on a slide. The ratio of sensitivity and specificity for CIN2 or worse of liquid-based relative to conventional cytology was calculated using pooled data from 9 studies (Arbyn, Bergeron et al. 2008). The ratio of sensitivity was 1.03 (95%CI= 0.97–1.09), p=0.002. Crude ratios of the odds of test positivity rates of liquid-based (n=49,222) compared with conventional cytology (n=40,562) for atypical squamous cells of undetermined significance or more severe was 0.95 (95%CI= 0.82-1.10) and the major advantage of liquid-based cytology was that it

resulted in fewer unsatisfactory tests (OR= 0.30, 95% CI= 0.23-0.38) (Siebers, Klinkhamer et al. 2008).

Specificity between the conventional and liquid based cytology is generally comparable and higher than that of the HPV testing. The specificity of the Pap test for detecting hgCIN 96.8% (95% CI, 96.3-97.3) was slightly higher than the specificity of the HPV test 94.1% (95% CI, 93.4-94.8), P<0.001) in the trial that reported Pap sensitivity of 55% (Mayrand, Duarte-Franco et al. 2007). The ratio of specificity between the HPV test and the Pap test was 0.91 (95%CI= 0.84–0.98), p<0.001 when the cut off was atypical squamous cells of undetermined significance or more severe (Arbyn, Bergeron et al. 2008).

The relative sensitivity of HPV screening in clinician versus self-collected samples

Numerous reports show that more hgCIN are identified in women when primary cytological screening is replaced by primary high-risk Human Papillomavirus (hrHPV) testing in cervical samples (Wright, Schiffman et al. 2004; Meijer, Berkhof et al. 2009; Anttila, Kotaniemi-Talonen et al. 2010; Ronco, Giorgi-Rossi et al. 2010). Sensitivities of detecting hgCIN between the HPV screening in self collected vaginal samples and standard liquid based cytology (LBC) are comparable (Lazcano-Ponce, Lorincz et al. 2011; Rijkaart, Berkhof et al. 2012). HPV screening in vaginal samples has a better sensitivity for the detection of high grade cervical intra-epithelial neoplasia or worse (CIN 2+), than the conventional Pap smear test (Lazcano-Ponce, Lorincz et al. 2011). A recent randomized trial in Mexican women of low socioeconomic status (Lazcano-Ponce, Lorincz et al. 2011) demonstrated self-sampling for HPV to be 3.4 times more sensitive than the conventional Pap smear test in detecting CIN2+. Hence, self-sampling for HPV testing appears to be more sensitive than the LBC for detecting high-grade CIN.

There is a high level of concordance between the clinician and self-collected samples for cervical HPV detection (Brink, Meijer et al. 2006). A meta-analysis of pooled data demonstrated concordance of 87% (0.82-0.91) with *kappa* 0.66 (0.56-0.76) between the clinician and self-collected samples for HPV detection (Petignat, Faltin et al. 2007).

Strategies that could increase the specificity of cervical screening

Secondary screening strategies such as genotyping for high-risk HPV types (Franceschi, Cuzick et al. 2009), short-interval repeat HPV testing (Gyllensten, Sanner et al. 2011), p16 testing (Samarawardana, Dehn et al. 2010; Jentschke, Lange et al. 2013), p16/Ki-67 double-staining

(Yoshida, Sano et al. 2011), DNA methylation techniques (Sun, Reimers et al. 2011; Snellenberg, De Strooper et al. 2012; Wentzensen, Sun et al. 2012; Lorincz, Brentnall et al. 2013; Mirabello, Schiffman et al. 2013), VIA (Sankaranarayanan, Esmy et al. 2007), LBC (Rijkaart, Berkhof et al. 2012; Rijkaart, Berkhof et al. 2012) and HPV mRNA detection (Rijkaart, Heideman et al. 2012; Chambers, Millan et al. 2013) were used in conjunction to increase the specificity of cervical samples.

Triaging self-collected HPV positive women to colposcopy

It is possible to apply some of these triaging methods to self-collected vaginal samples (Yoshida, Sano et al. 2011) (Jentschke, Lange et al. 2013). Reflex cytology of HPV positive is possible for cervical samples, but it is not an appropriate option for self-collected specimens. Among women older than 35 years, primary HPV DNA screening with cytology triage was more specific than conventional screening (Leinonen, Nieminen et al. 2009). Triaging high risk HPV-positive women with cytology, followed by repeat cytology testing yielded a high NPV and modest colposcopy referral rate and appeared to be the most feasible management strategy out of 14 different triaging strategies evaluated (Rijkaart, Berkhof et al. 2012). The specificity can be increased by the cytology triage of cervical samples (Gok, Heideman et al. 2010). A vast majority (684/757= 90%) of women who were screened positive for HPV self-testing studies attended subsequent follow-up (Gok, Heideman et al. 2010).

The principles of triaging vaginal HPV positives are similar to that of the cervical HPV positives, as long as the sample used to triage is a cervical sample. The main aim of triaging HPV positives is to increase the specificity of the screening test. It is important to pick up a good positive surrogate marker of cervical disease as the triaging method. The most reliable method would be to test a cervical sample, aiming to identify one or more surrogate markers of cervical neoplasia.. A vast majority of vaginal HPV positives attended for a cervical smear in many reported studies. In a large community-based self-sampling study conducted in The Netherlands (Gok, Heideman et al. 2010), 27% out of 27,792 women who did not go for their routine smears, self-obtained a vaginal specimen for HPV testing, at home. Ninety percent (684/757) of HPV positive women attended subsequent smear test. Similar HPV+ follow-up smear uptake was reported from the same study group in another large scale, population based study in The Netherlands which recruited 26,409 defaulters(Gok, van Kemenade et al. 2012). All HPV positives 8/8 (100%) had a smear test in the Szarewski 2011 study (Szarewski, Cadman et al. 2011). A lower proportion 7/10 (70%) of HPV positives had a smear in the Darlin 2013 study

(Darlin, Borgfeldt et al. 2013). It was probably the lowest in a study based in France where 116/283= 41% came for cytology follow-up. Women who were living in the Bouches du Rhone area and had not had a Pap test in the previous 2 years who did not respond to the first invitation were the target population of this study. A shorter screening interval may have contributed to lower attendance at the follow-up visit. Another French study (Tamalet, Le Retraite et al. 2013) had a follow-up rate of 43/62= 69%. In France, about 40% of women aged 25-65 years do not participate in regular screening.

Recognising specific molecular markers in the self-collected material is another way of increasing the specificity. Isolation of HPV 16 in self-collected samples could increase the specificity (Daponte, Pournaras et al. 2006). Molecular markers indicative of active HPV disease is another approach (Yoshida, Sano et al. 2011), however, poor cellularity is an important limitation. The feasibility of identification of cyclin-dependent kinase inhibitor 2A protein [p16 (INK4a)] on self-collected cervico-vaginal lavage samples to improve specificity was evaluated in 140 women (Jentschke, Lange et al. 2013). Whilst 27 (19%) physician-collected samples were p16 (INK4a) ELISA positive, only one (1%) vaginal lavage sample self-collected with the Delphi screener was positive. Another study comparing HPV mRNA with HPV DNA testing found mRNA testing to increase the specificity of vaginal self-sampling slightly (93.0% [91.8, 94.0] vs 90.5% [89.1, 91.7]) for identical levels of sensitivities of 62.5% [35.4, 84.8] to detect CIN3+ (Nieves, Enerson et al. 2013).

The low specificity of an HPV DNA test may lead to psychological distress, emotional distress, social distress, increased frequency of follow-up and most importantly, the possibility of over treatment (Leinonen, Nieminen et al. 2009). Specificity of HPV screening for detection of hgCIN is lower compared with conventional cytology (Cuzick, Clavel et al. 2006; Shi, Belinson et al. 2009; Ronco, Giorgi-Rossi et al. 2010). The lower specificity observed in younger women may be explained by the high prevalence of transient HPV infections. It is suggested that women who have tested positive for hrHPV but negative for cytology should have co-testing in 1 year intervals (Bulkmans, Berkhof et al. 2007; Naucler, Ryd et al. 2007). This strategy may reduce the number of colposcopy referrals (Cuzick, Arbyn et al. 2008; Franco, Mahmud et al. 2009; Zhao, Florea et al. 2010).

Acceptability of self-sampling

The acceptability of self-sampling has been evaluated in many studies. Self-sampling has been generally well accepted. Acceptability rates of 75% (Jones, Wiegerinck et al. 2008), 86% (Safaeian, Kiddugavu et al. 2007), 88% (Nobbenhuis, Helmerhorst et al. 2002) and 93% (Dzuba, Diaz et al. 2002) have been reported. The majority of women found self-sampling devices easy to use, less embarrassing, more relaxed and more comfortable than clinician sampling. Although women's response to self-sampling was generally positive, many were uncertain whether they had collected an adequate sample (Nobbenhuis, Helmerhorst et al. 2002; Barata, Mai et al. 2008). A large proportion of women from Indian and African-Caribbean ethnic groups living in Manchester who self-collected were concerned about doing the test properly (Forrest, McCaffery et al. 2004). A lack of understanding about the difference in principles of cytology screening and HPV screening could have played a part in this. Cultural and religious beliefs do not appear to have been barriers in accepting self-sampling for HPV screening (Howard, Lytwyn et al. 2009; Barbee, Kobetz et al. 2010). Overall, most studies showed that women preferred self-collection over clinician collection, suggesting that self-sampling has the potential to increase the population coverage (Dzuba, Diaz et al. 2002; Jones, Wiegerinck et al. 2008).

Self-sampling uptake may depend on many factors such as,

a) overall smear coverage of the population
b) duration since the last smear test
c) age and attitude of the defaulter
d) reason for defaulting
e) method and the quality of the information provided
f) type of self-sampling device
g) method, the way (how much the woman like the test) and time of approach
h) how cumbersome was the consent procedure
i) planned method of follow-up
j) trustworthiness of the service provider
k) how strong is the existing evidence to convince defaulters
l) availability of someone familiar who had experienced this (recommendation by a peer or family member who has done self-sampling)
m) availability of self-sampling at a different time when circumstances had been changed as some defaulters may take a long time to decide and may need to be reminded

The potential for self-sampling to increase the screening coverage

Offering self-sampling to screening programme defaulters is known to increase the population's screening coverage. All nonparticipants in organized cervical cancer screening in 2008 in Espoo, Finland were randomized to receive a self-sampling kit (n=1,130) or a reminder letter (n=3,030) (Virtanen, Anttila et al. 2011). The screening participation rate in the self-sampling arm, 30%, was significantly higher than in the reminder letter arm, 26%. The screening coverage rose significantly after the two interventions from 64% to 75%. The same research group's larger study randomized 8699 defaulters to receive either a self-sampling kit (2,397 women) or an extra invitation (6,302 women) (Virtanen, Nieminen et al. 2011). The adjusted relative risk for taking up a screening test was 1.21 (95% CI: 1.13–1.30) when self-sampling was offered as the second intervention in comparison to sending a cytology reminder letter. Total attendance increased from 65% to 76% by self-sampling and from 65% to 74% with a reminder letter. Combining the interventions (a reminder letter and then self-sampling) increased total attendance from 63% to 78%.

The evidence supporting clinical applications of self-sampling

Offering self-sampling has been shown to be superior to a routine recall invitation for LBC in re-attracting defaulters into the screening program in developed countries (Virtanen, Anttila et al. 2011). Additionally, self-testing has been shown to facilitate access to cervical screening for women in low resource areas (Lazcano-Ponce, Lorincz et al. 2011) (Belinson, Du et al. 2011) (Belinson, Du et al. 2012).

According to a recently published review (Snijders, Verhoef et al. 2013), which included studies published between January 1992 and January 2012, comparing clinical accuracy of HPV testing on self-sampled material with that of cytology or HPV testing on clinician-taken samples, hrHPV testing on self-samples appeared to be at least as, if not more, sensitive for detecting CIN2+ as cytology on clinician collected cervical samples.

According to the first published systematic review and meta-analysis to determine the accuracy of testing for HPV DNA in urine in detecting cervical HPV in sexually active women (Pathak, Dodds et al. 2014), testing urine for HPV seems to have good accuracy for the detection of cervical HPV. Urine detection of high risk HPV had a pooled sensitivity of 77% (68% to 84%) and specificity of 88% (58% to 97%). The authors concluded that when cervical HPV detection is considered difficult, urine testing should be regarded as an acceptable alternative.

LITERATURE REVIEW

a) Search strategy

Key words and Medical Subject Headings (MeSH) used:
Human Papillomavirus, papillomavirus infections, HPV testing, HPV test*,self-test*, self-testing, self-sample, self-sample*, self-collect*, physician-collect*, physician taken, clinician collect*, clinician obtained, provider-obtained, home testing, auto-test, vaginal smear, unscreened, under screened, non-attendance, non-compliance, patient compliance, patient participation, screening coverage, uptake rate, cervix, cervical cancer prevention, cervical screening, HPV screening, smear test, Pap test, liquid based cytology and cytology. Cervical neoplasms, uterine cervix carcinoma, cervical intraepithelial neoplasia and cervical carcinoma in-situ. Various combinations of search words/*stems were used to search titles and abstracts. Relevant author names were also searched.

Databases: PubMed database was searched through EndNoteX5 software. Evidence published in the last 2 decades (from 1990) was focussed on. Only evidence published in the English language was included.

Moreover, abstract books of the 2011 International Papillomavirus Conference held in Germany (17-22 Sep), EUROGIN 2012 (Prague 8-11 July) and EUROGIN 2013 (Florence 3-6 Nov) were searched manually. Reports of the National Cervical Screening Programme were accessed manually. Research of some dedicated study groups and author names were also searched. References of relevant publications were also retrieved.

Inclusion criteria: Studies in which the HPV testing has been carried out as a part of cervical screening or understanding the natural history of the cervical disease. Relevant systematic reviews and meta-analysis were also included.

Exclusion criteria: Studies in which HPV testing had been carried out for purposes other than cervical screening, e.g. to determine the HPV prevalence in male partners of sexually active women or other HPV related diseases.

Over 600 abstracts were reviewed. Manuscripts of relevant abstracts were retrieved.

b) Themes under which the literature review was organised

1. Is self-sampling for HPV testing an effective screening strategy?
2. Could self-sampling increase the cervical screening participation in high income countries?
3. Reasons for non-participation of cervical screening programmes.
4. Different self-sampling kits used.

1.2 Is self-sampling for HPV testing an effective screening strategy?

HPV screening in self collected vaginal samples

Early research on self-sampling was mainly based on women attending colposcopy clinics. The primary aim of most of these studies was to demonstrate the concordance between the clinician collected and self-collected samples for HPV screening. Almost all of these studies used colposcopic diagnosis as the reference standard although positive lesions were confirmed by histology (biopsies were not taken when the cervix was colposcopically normal).

In one study, the overall agreement between self-collected and clinician-collected samples was 92%; however among HPV-positive specimens, the HPV agreement was only 39% (Harper, Hildesheim et al. 1999). In another, the HPV prevalence in the vagina (21%) was slightly higher than the cervix (18%), when a swab was used for self-collection (Bidus, Zahn et al. 2005) in women younger than 50 years. The prevalence was similar (10% vs 9%) in women over 50 years old. A study was conducted to compare time of clearance of specific HPV types between clinician collected lavage and self-collected sampling in a cohort of 537 women (Moscicki, Widdice et al. 2010). Both samples were obtained every 4 months at alternate 2-month windows. Findings suggest that self-collected vaginal swabs reveal similar natural histories of

HPV compared to clinician collected lavage specimens making self-testing a feasible method for repeated HPV DNA detection.

In a population based study which included 878 sexually active Brazilian women aged 15-69 years (Ogilvie, Patrick et al. 2005), the hrHPV prevalence was 34% in self- collected Digene brush samples, compared with 29% among clinician collected samples. In 82 (9%) participants, the self-collected sample tested positive for HPV HC II, whereas the clinician collected sample tested negative. Conversely, 35 (4%) patients tested positive in clinician collected samples and negative in their self-collected samples (kappa=0.7). All 878 participants underwent colposcopy. Biopsy was taken as indicated (n=63). Of 9 cases of histologically-confirmed, high-grade squamous intraepithelial lesion, self-collected and clinician collected samples missed one each.

Self-collected dry samples appear as good as wet sample for HPV screening (Stainier and Cornelis 1998; Cambronne and Schneewind 2002; Darlin, Borgfeldt et al. 2013). The FTA Elute cartridge, which does not require any liquid preservative transport medium (Cambronne and Schneewind 2002; Geraets, van Baars et al. 2013; Guan, Gravitt et al. 2013) appears to be a promising method of specimen transport, if cervical cancer screening programs consider using the use of self-collected specimen for HPV testing.

Some studies correlated the clinical performance between the self-collected vaginal samples and clinician collected cervical cytology samples. Studies conducted by (Wright, Denny et al. 2000; Belinson, Qiao et al. 2003) (Belinson, Qiao et al. 2001) and (Salmeron, Lazcano-Ponce et al. 2003) had a large number of participants (1365-8497). All 1997 women in Belinson's 2001 study had undergone colposcopy. The Dacron swab was used as the self-sampler except in Belinson's 2003 study which used a vaginal conical (cytology) brush. This study was the only study which used liquid based cytology for cytology screening. The other 3 studies used conventional smears where the specimen was collected with a spatula. The sensitivity of the cytology screening arm was less than that of the HPV screening arm in all studies.

However, diagnostic accuracy of HPV screening between the clinician collected samples for detecting high grade pre-cancer has been the focus of some researchers. The number of participants in most of these studies was 200 or less (Morrison, Goldberg et al. 1992; Morrison, Goldberg et al. 1992; Sellors, Lorincz et al. 2000; Harper, Noll et al. 2002; Nobbenhuis, Helmerhorst et al. 2002; Kahn, Slap et al. 2004; Brink, Meijer et al. 2006; Castle, Aftab et al.

2006; Daponte, Pournaras et al. 2006; Seo, Song et al. 2006; Szarewski, Cadman et al. 2007; Dijkstra, Heideman et al. 2012; Jentschke, Soergel et al. 2013). Some studies had 200-300 participants (Hillemanns, Kimmig et al. 1999; Gravitt, Lacey et al. 2001; Lorenzato, Singer et al. 2002; Garcia, Barker et al. 2003; Khanna, Mishra et al. 2007; Twu, Yen et al. 2011). All of these large studies used the Hybrid Capture II (HC2) for detecting high risk HPV DNA.

The HC2 test was the most commonly used HPV DNA test. It was the DNA test of choice for cervical samples (Nieminen, Vuorma et al. 2004). It performed consistently well (Gage, Partridge et al. 2011; Arbyn, Roelens et al. 2013). However, the HPV detection was 17% lower in self collected specimen in comparison to clinician collected cervical samples when HC2 had been used (Belinson, Hu et al. 2010). A total of 397 out of 2,625 women tested positive for hrHPV with HC2 in any of 5 samples obtained. All hrHPV positive samples were also tested with the Linear Array (a PCR based) assay. Of 47 women with CIN 2+, HC2 was positive in (46/47=98%) of endocervical and (38/47=81%) of self-collected specimens. Seven out of 9 women with CIN2+ and a negative self-collected HC2 tests were positive for hrHPV by the Linear Array on the self-collected sample. According to expert opinion (Arbyn, Verdoodt et al. 2014), PCR based tests are preferred as the test of choice for self-collected samples. It would be interesting to know sensitivity data of self-sampling trials, if PCR based tests were used as the reference standard rather than signal amplification tests such as HC2 or Cervista. Self-sampling trials which used multiple HPV tests (Belinson, Du et al. 2011) provide some supporting evidence for this.

Based on the evidence built on the women referred to colposcopy, large scale population-based studies were carried out.

Table 1.2.1: Applied, clinical research carried out in normal screening population in low and medium income countries to evaluate the feasibility of self-sampling.

Study	Country	n (age group)	Self-sampling Device	HPV test
(Salmeron, Lazcano-Ponce et al. 2003)	Mexico	7868 (15-85)	Dacron swab (self), Conical brush (clinician)	HC2
(Qiao, Sellors et al. 2008)	China	2,530 (30-54)	QIAGEN conical brush	*c*HPV
(Belinson, Du et al. 2011)	China	2,653 (16-54)	QIAGEN conical brush	HC2
(Lazcano-Ponce, Lorincz et al. 2011)	Mexico	22,102 (25-65)	Digene conical brush	HC2
(Nieves, Enerson et al. 2013)	Mexico	2,049 (30-50)	POI/NIH sampler	HC2 AHPV
(Sankaranarayanan, Nene et al. 2009)	India	34,126 (30-59)	Digene conical brush	HC2
(Bhatla, Dar et al. 2009)	India	546 (>30)	Digene conical brush	HC2
(Sowjanya, Paul et al. 2009)	India	432	Digene cervical sampler	HC2 PCR
(Chang, Tseng et al. 2002)	Taiwan	1194	?Dacron swab	HC2

Abbreviations: *c*HPV= *care*HPV test; AHPV= Aptima HPV DNA test.

The Digene/QIAGEN conical brush was the self-sampler used in all except 2 studies in (Table 1.2.1). The other 2 studies used swabs. Two studies were on a much larger scale, including over 34,000 (Sankaranarayanan, Nene et al. 2009) and 22,000 (Lazcano-Ponce, Lorincz et al. 2011) participants. The former study was designed to have 80% power at the 5% significance level to detect a 50% reduction in cumulative mortality rate from cervical cancer within 15 years of enrollment between one of the arms and the control group.

The latter targeted a sample size of 9500 women per group (initial refusal rate of up to 25% predicted) providing 85% power to show a 40% difference (two-sided alpha of 0·05) between groups. The study was aiming to assess relative detection rates, relative sensitivity (ratio of the

relative detection rates), positive predictive value for CIN 1–3 and invasive cervical cancer in the HPV group versus the cytology group. They reported that HPV testing of self-collected samples had a relative sensitivity of 3·4-times greater (95% CI, 2·4–4·9) than cytology for detection of CIN 2 or worse; it detected 41·1 times (95% CI, 15·2–111·2) more CIN 1; 3·6 times (95% CI, 2·2–6·0) more CIN 2; 2·4 times (95% CI, 1·1–5·1) more CIN 3; and 4·2 times (95% CI, 1·9–9·2) more invasive cancer than did cytology. A sample was taken from the ectocervix with an Ayre wooden spatula, and specimens from the endocervical canal taken with a cytobrush were smeared onto one slide and sent to one diagnostic reference centre in each state. Only 38/11,054 (0.3%) Pap smears were reported positive, over 10 times lower than cervical cytology results in the UK (NHSCSP 2012; Health and Social Care Information Centre 2013). Whilst 4 CIN1, 20 CIN2, 10 CIN3 and 8 cancers diagnosed had a positive cytology result, 137 CIN1, 60 CIN2, 20 CIN3 and 28 cancers diagnosed had a positive HPV result. It appears that the poor sensitivity of the conventional cervical smear may have contributed to such a high relative sensitivity of HPV screening rather than exceptionally high quality of HPV screening methods.

The HC2 test was used to test self-collected samples, except in one study which used *care*HPV (*c*HPV), a new test (*care*HPV; QIAGEN, Gaithersburg, MD, USA) developed to detect 14 hrHPV to screen women in developing regions. The *care*HPV test is broadly based on the HC2 test with some important differences. The assay time is 2.5 h or less, compared with up to 6 h for HC2. The *care*HPV collection medium, unlike other collection media, contains no toxic chaotropic salts, but rather contains non-toxic surfactants and is specifically formulated for absorbing cervical specimens from the collection brush without any requirement for extended mechanical shaking. All 2388 women were assessed by visual inspection with acetic acid (VIA), Digene High-Risk HPV HC2 DNA Test (HC2), liquid-based cytology (LBC), and colposcopy with directed biopsy and endocervical curettage as necessary(Qiao, Sellors et al. 2008). Of note, 441 women with negative colposcopy, but unsatisfactory or abnormal cytology or who were positive on HC2 or the new *care*HPV test, were recalled for a second colposcopy, four-quadrant cervical biopsies, and endocervical curettage. The sensitivities and specificities for detecting CIN2+ (n=70) of the *care*HPV test were 90·0% (95% CI 83·0–97·0) and 84·2% (82·7–85·7), respectively, on cervical specimens, and 81·4% (72·3–90·5) and 82·4% (80·8–83·9), respectively, on vaginal specimens; compared with VIA 41·4% (29·9–53·0) and 94·5% (93·6–95·4). It appears that the *care*HPV test is a good HPV test for low-resourced settings.

One study (Nieves, Enerson et al. 2013) used a HPV mRNA - Aptima HPV test (AHPV), reporting the sensitivity of LBC (>ASCUS), HC2 and AHPV for CIN3+ (n=16) in clinician collected sample as 88%, 100%, and 100%, respectively. The specificity of LBC (>ASCUS), HC2, and AHPV for CIN3+ was 94%, 92%, and 94%, respectively. The sensitivity of vaginal self-collected samples for CIN3+ was very low 63% (95%CI= 35.4, 84.8) in self-collected vaginal samples in HC2 as well as in AHPV. The specificity of vaginal samples was significantly higher in the AHPV test 93.0 (95%CI= 91.8, 94.0) in comparison to the HC2 test 91% (95%CI= 89.1, 91.7). It appears that HPV mRNA testing gives a more specific result than HC2 without compromising its sensitivity. Sensitivity of LBC which was carried out in a center in the USA was higher than that of self-samples for HPV testing.

HPV screening in urine samples

Urine is essentially a self-collected sample. Urine sample collection is used routinely for molecular testing in the diagnosis of the most common sexually transmitted infection (STI), for example, infections with *Chlamydia trachomatis* (Carder, Robinson et al. 1999) and *Neisseria gonorrhoeae*. Self-sampling for STI has increased patient acceptance of STI screening tests in the UK, which lead to development of the national Chlamydia Screening Programme in England www.chlamydiascreening.nhs.uk. Similarly, a urine-based assay designed for the detection of HPV DNA has been utilized previously in groups at high-risk of infection, such as subjects infected with HIV. Willingness to access self-collected tests for STIs (85%) and HIV (87%) was high (Saunders, Mercer et al. 2012).

Some principles of HPV screening and Chlamydia screening appear similar, as both infect the female genital tract, particularly the cervix in a similar way, although the treatments vary. Sensitivities of detecting Chlamydia by Cobas 4800 PCR method (Roche diagnostics, USA) are comparable between urine (Carder, Robinson et al. 1999), self-collected vaginal and clinician-collected cervical samples, all of which are over 90% (manufacture's literature). A urine sample is probably the most easily self-collected biological sample, worldwide. In a colposcopy clinic based study (Sellors, Lorincz et al. 2000), almost all respondents (126/128= 98%) deemed urine sampling acceptable, 93% (118/127) found vulvar sampling acceptable, and 88% (112/127) found vaginal sampling acceptable. Therefore, it is worth exploring clinical applications of HPV screening in urine samples in terms of preventing cervical cancer as clinician sampling or vaginal self-sampling may not be acceptable for some communities in the world.

Table 1.2.2 Studies evaluated the clinical applications of HPV screening in urine samples

Author, year	Country	Subjects, age (scatter)	Amplification/ primers	hrHPV DNA positive
(Sellors, Lorincz et al. 2000)	Canada	200 women with abnormal cytology 32 (SD=9)	HC II; PCR consensus HPV L1 primers and β-globins	30% (43/142) No HSIL 45% (26/58) HSIL
(Stanczuk, Kay et al. 2003)	Zimbabwe	43 women with cancer 44 (24-70)	Conventional nested PCR, degenerated nested primers	72% (31/43) cancer
(Daponte, Pournaras et al. 2006)	Greece	77 women with abnormal cervical cytology	PCR & commercial multiplex assay	32% (25/77) overall 45% (13/29) HSIL 88% (8/9) cancer
(Gupta, Arora et al. 2006)	India	30 women with cancer & 30 healthy controls 42	HPV-L1 consensus primer & in-house beta-globin primers	27% (8/30) control 82% (23/28) cancer
(Manhart, Holmes et al. 2006)	USA	3262 sexually active women (18-25)	PCR,MY09/MY11/ HMB01 & PC04/ GH20 β-globin	29% (934/3262) overall
(Alameda, Bellosillo et al. 2007)	Spain	50 women referred to gynae clinic 36 (28-55)	In-house or commercial PCR MY09/MY11	6% (1/36) LSIL 82% (10/14) HSIL
(Feng, Hawes et al. 2007)	Senegal	129 women with cervical biopsies 47 (SD=11)	PCR MY09/MY11/ HMB01 & PC04/ GH20 β-globin	11% (2/19) No CIN 44% (4/9) CIN1 59% (17/29) CIN2+ 70% (50/72)cancer
(Song, Lee et al. 2007)	Korea	89/100 women with cervical biopsies and cervical swabs 45 (26-77)	PCR –based DNA microarray system-HPV DNA chip	13% (3/23) cervicitis 62% (26/42) HGCIN 71% (17/24) cancer
(Payan, Ducancelle et al. 2007)	France	333 women referred to Gynaecology	Real-time PCR. Mx4000 (Stratagene) vs LightCycler (Roche)	37% (66/177) overall in urine, 45% (150/333) in cervix (k=93%)

(Daponte, Tsezou et al. 2008)	Greece	100 women with abnormal cytology & HPV-16 positive	Classic PCR & QRT PCR	33% (16/49) LSIL 72% (26/36) HSIL 87% (13/15) cancer
(Fambrini, Penna et al. 2008)	Italy	52 HG-CIN before CO_2 conization 38 (18-59)	PCR kit Bioline	81% (42/52) HGCIN Relative sensitivity (urine vs cervix) 96.6%
Payan et al. 2009	France	1,169 women refusing smears (25-65)	Real-time PCR	19% (222/1169) overall
(O'Leary, Sinka et al. 2011)	Scotland	2575 unvaccinated school girls (11-18)	HPV Inno-LiPA (PCR)	weighted prevalence 1% (11-14 years) 15% (16-18 years)
(Cuschieri, Nandwani et al. 2011)	Scotland	90 women attending at drop-in sexual health clinic (16-25)	PCR based assay	Relative sensitivity (urine vs cervix) 90.5% (79.3-96.9) Relative specificity 67.6% (50.2–82.0%)
(Mendez, Romaguera et al. 2013)	USA	52 women attending Gyne clinic (21-60)	Linear Array (PCR)	42% (22/52) urine 67% (35/52) cervix
(Kavanagh, Sinka et al. 2013)	Scotland	378 Screening defaulters were sent urine collection kits (20-21)	Digene HPV Genotyping RH test GP5 + 6+ primers	weighted prevalence 32% (adjusted OR= 0.33 (95%CI: 0.25,0.44)
(Tanzi, Bianchi et al. 2013)	Italy	107 women attending STD clinic (22-70)	PCR based assay (RFLP for typing). MY09/11primers	65% (69/107) 95% CI: 55-73%. Relative sensitivity (urine vs cervix) 98.6% (93.1–99.9%) Relative specificity 97.4% (87.7–99.9)

Abbreviations: STD= sexually transmitted disease.

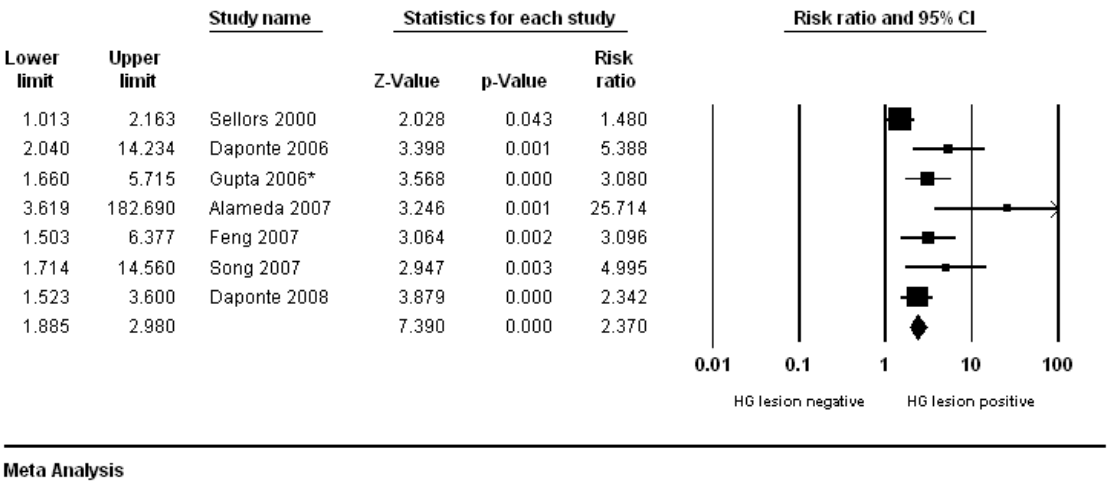
Table 1.2.2 summarises studies evaluating HPV testing of urine samples. All except one study (Sellors, Lorincz et al. 2000) used a PCR based assay. High risk HPV was detected by HC 2 in the self-collected vaginal samples of 50/58 (86.2%), in the self-collected vulvar samples of

36/58 (62.1%), and in the self-collected urine samples of 26/58 (44.8%) and physician collected cervical samples of 57/58 (98.3%) in this study.

Urine is a diluted specimen, not only are HPV DNA levels in urine low, but also it contains polymerase chain reaction (PCR) inhibitors (Khan, Kangro et al. 1991) such as urea and nitrites. Moreover, HPV DNA levels can be affected by bacterial contamination and endonucleases that could be found in urine specimen (Carder, Robinson et al. 1999; Milde, Haas-Rochholz et al. 1999). All these factors can potentially reduce the sensitivity of the test.

Seven studies in the Table 1.2.2 contain urine HPV prevalence data in women with high grade cervical lesion and ones without. I have carried out a meta-analysis of these data (Fig 1.2.1). It computes that the relative risk of HG HPV to be found in urine samples of women with a high grade CIN lesion is 2.4 (95CI, 1.9-3.0).

Fig 1.2.1: Urine HPV positivity in women with high grade CIN



Although the genomic DNA found in urine samples appears to be very low (Payan, Ducancelle et al. 2007; Mendez, Romaguera et al. 2013), detection is possible, if the highly effective PCR-based method, restriction fragment length polymorphism (RFLP) has been used with a newly designed specific primer set (Tanzi, Bianchi et al. 2013). The restriction fragment length polymorphism (RFLP) technique has shown some promising results in previous urinary HPV screening studies. Tanzi (2013) reported a very high relative sensitivity of detecting HPV in cervical versus urine samples 98.6% (93.1– 99.9%) and a relative specificity of 97.4% (87.7–99.9%), with a very high NPV of 97.4% (87.7–99.9%) for HPV DNA detection in urine versus

cervix samples,. Another highly sensitive and quantitative general HPV DNA real-time PCR method reported an excellent (93%) kappa agreement for HPV DNA between cervical and urine specimens (Payan, Ducancelle et al. 2007). The relative sensitivity of urine versus cervical sampling for HPV detection was 90.5% (79.3-96.9) when a highly sensitive PCR method had been used (Cuschieri, Nandwani et al. 2011). The relative specificity was 67.6% (50.2–82.0%). Fambrini (Fambrini, Penna et al. 2008) reported the relative sensitivity of 96.6%.

A pilot study in France (Payan, Ducancelle et al. 2007) showed that the response rate of women who had been invited for a cervical smear examination substantially increased when they were offered the option of urine sampling for HPV screening. Whilst 312/5781(5.4%) participants in this study accepted cervical smear invitation, 1169/4036 (29%) accepted urine sampling for HPV screening.

Although it appears that HPV testing in urine sample has the potential to be a surrogate marker of cervical HPV infection, more applied research is required before it can be offered as a primary screening tool. Moreover, DNA extraction and testing appears more complex than modern, automated, high throughput assays. Two studies that reported very high relative sensitivities (91.5% and 98.6%) of detecting HPV between the urine and cervix seem promising

2. Could self-sampling increase cervical screening participation in high income countries?

Since 2007 a number of applied research studies have been carried out – these are summarised in Table 1.2.3. The primary aim of most of these studies was to see if offering self-sampling to screening programme defaulters would increase the screening attendance.

Table 1.2.3 Population-based clinical research on self-sampling in high-income countries

No	Study	Country (screening coverage %)	n (age) Not screened for*	Self-sampling Device	HPV test	Self-test uptake (%)	HPV positivity (%)	HG-CIN (%)
1	(Stenvall, Wikstrom et al. 2007)	Sweden (Uppsala) (70)	369 (35-50) 6 years	Qvintip	HC2	31.7	26	3
2	(Bais, van Kemenade et al. 2007)	Netherlands (63)	2,546 (30-50) 2 invita*	Viba brush+ UCM	PCR	31.3	8	1.7
3	(Sanner, Wikstrom et al. 2009)	Sweden (39-60)	2,829 (30-58) 6 years	Qvintip	HC2	39.1	6.7	1.2
4	(Gok, Heideman et al. 2010)	Netherlands (77)	28,073 (30-60) 2 invita*	Delphi Screener	HC2	27.5	10.3	1.3
5	(Gok, Heideman et al. 2012)	Netherlands (77)	26,409 (30-60) 2 invita*	Viba brush	HC2	30.8	8.3	2.5
6	(Georgi Rossi, Marsili et al. 2011)	Italy (67-70)	2,480 (35-64) 2 invita*	Pantarhei sampler	HC2	'Letter'= 5.8 'Clinic'= 12.5 'Kit'= 16.7	3.6	0.0
7	(Wikstrom, Lindell et al. 2011)	Sweden (39-60) (70)	4,060 (39-60) 6 years	Qvintip	HC2	39.0	7	1
8	(Lindell, Sanner et al. 2012)	Sweden (39-60) (70)	3,618 (50-65) 6 years	Qvintip	HC2	39.4	4.6	0.7
9	(Gyllensten, Sanner et al. 2011)	Sweden (39-60) (70)	7,331 (30-65) 6 years	Qvintip	HC2	39	6.6	1.5
10	(Virtanen, Anttila et al.	Finland (70)	1,130 (30-60)	Delphi Screener	HC2	29.8	No data	No data

	2011)		5 years					
11	(Virtanen, Nieminen et al. 2011)	Finland (70)	2,397 (30-60) 5 years	Delphi Screener	HC2	31.5	12	1
12	(Piana, Leandri et al. 2011)	France (60)	4,400 (35-69) 1 invita*	?flocked swab	PCR	26	6.2	0.4
13	(Szarewski, Cadman et al. 2011)	UK (London) (68)	1,500 (25-64) 2 invita*	Dacron swab	HC2	6.4	5.2	2.0
14	(Castle, Rausa et al. 2011)	USA (Mississip pi Delta)	119 (25-65) 3 years	Fournier device	HC2	52.1	14.5	No data
15	(Tamalet, Le Retraite et al. 2013)	France (60%)	3767 (35-65) 1 invita*	flocked swab	PCR	25.1	6.6	0.3
16	(Darlin, Borgfeldt et al. 2013)	Sweden (Lund) (75%)	1000 (32-64) 9 years	Cotton swab	PCR	14.7	6.9	0.0

PCR= polymerase chain reaction, invita= invitation, *these women had not been screened for at least (number of) years or did not respond after (number of) Invitations to attend screening, 'letter'= letter was sent to order a kit, 'clinic'= a clinic appointment was sent to discuss screening choice, 'kit'= a self-sampling kit was directly mailed to the woman.

The effectiveness of detecting HPV infected cervical cells may vary between samplers, and different populations. Therefore, the heterogeneity of results in Table 1.2.3 should not be surprising.

All except one (the USA) of these high-income countries have established cervical screening programmes (Anttila, Ronco et al. 2004). The cervical screening coverage in countries that these studies were conducted is between 60% (France) and 77% (The Netherlands) although the mode is 70%. Although there is no programme in the USA, coverage is estimated to be as great (i.e. over 70%).

Two very large scale, population based RCTs were conducted in the Netherlands, including 28,000 defaulters in 2010 and 26,000 in 2012 by Gök.

The most frequently used self-sampler was the Rovers Viba brush. Other self-samplers used in order of frequency were: Qvintip, swab (Dacron/flocked/cotton), Delphi Screener, Pantarhei sampler and Fournier device. The Darlin study (Darlin, Borgfeldt et al. 2013) described the device used as a "cotton swab". The prevalence of hrHPV was 10/145 (6.9%) and no HSIL was found in 7 out 10 HPV+ women who attended cervical cytology, although the cytology of one woman who had had a hysterectomy was reported as LSIL. If the swab was indeed made from cotton, it could potentially have inhibited HPV DNA detection which may have contributed towards not finding any cervical dyskaryosis in this cohort of 147 women. The main author of this study, Lotten Darlin, was contacted to clarify this. She confirmed that they had used a cotton swab.

The self- sampling uptake rate in 16 studies is summarised in Table 1.2.3. It varied between 5.8% and 39.4%. The uptake rate (52.1%) of a study by Castle (Castle, Rausa et al. 2011) has been excluded from analysis as researches asked eligible women's consent in their homes, which may have influenced women's choice. The mean is 26.3% (95%CI, 20.4-32.0). The median was 29.8% with IQR=15.7-35.4%. The self-sampling uptake rates (31.7%-39.4%) were highest in Swedish studies where Qvintip had been used (Stenvall, Wikstrom et al. 2007; Sanner, Wikstrom et al. 2009; Gyllensten, Sanner et al. 2011; Wikstrom, Lindell et al. 2011; Lindell, Sanner et al. 2012). By contrast, the only Swedish study that did not use Qvintip (Darlin, Borgfeldt et al. 2013) reported one of the lowest uptake rates in self-sampling (6.9%). Two studies conducted in Finland reported self-sampling uptake rates around 30% (Virtanen, Anttila et al. 2011; Virtanen, Nieminen et al. 2011). The uptake rates were 27.5% (Gok, Heideman et al. 2010), 30.8% (Gok, van Kemenade et al. 2012) and 31.3% (Bais, van Kemenade et al. 2007) in 3 Dutch studies. The uptake rate was 26% in one French study (Tamalet, Le Retraite et al. 2013). The UK study (Szarewski, Cadman et al. 2011) reported the lowest self-sampling uptake rate of 6.4%. Many factors account for the variance of self-sampling uptake observed in these studies. It appears that the self collection uptake rate depends on the type of self-sampling device, geographical location of the study population and the way that self- sampling has been offered.

High risk HPV positive rate in self collected vaginal samples was reported in all but one study. It varied between 3.6% and 26.0%. The mean was 8.8% (95%CI, 5.8-11.9), the median was 6.9% with IQR=6.2-10.3%. Of the four studies with over 10% positive for hrHPV, two used the Delphi

screener 10.3% (Gok, Heideman et al. 2010), 12% (Virtanen, Nieminen et al. 2011); one used the Fournier device 14.5% (Castle, Rausa et al. 2011) and the one used Qvintip 26%. Prevalance of hgCIN, which was reported in all but the last study, was 1.3%, 1.0% and 3.0%, respectively.

The prevalance of hgCIN was reported in 14/16 studies.. It varied between 0.0% and 3.0%. The mean was 1.2% (95%CI, 0.7-1.7). The median was 1.1% with IQR=0.4-1.8%. There was a significant correlation between the hrHPV positive rate and the prevalance of hgCIN (Pearson Correlation 0.634, P=0.014 two-tailed) The prevalance of hgCIN in these studies is comparable with that of the cervical cytology based population screening in England (Health and Social Care Information Centre 2013)

HPV screening in self-collected samples appears to be a pragmatic method of increasing cervical screening coverage. Authours of an Italian self-sampling study (Giorgi Rossi, Marsili et al. 2011) predicted that self-sampling could have the potential to increase cervical screening coverage in urban areas such as Rome and Florence up to 90%, if self-sampling increased the overall coverage by 5%. Increasing the screening coverage by 5% appears to be somewhat optimistic as some interventions were able to increase cytology screening coverage only by 1.3% (95%CI= -3-2.9) (Eaker, Adami et al. 2004); 0.4%-1.3% (Corkrey, Parkinson et al. 2005) and 0.94% (95% CI 0.21% to 1.67%) at 6 months (Jensen, Svanholm et al. 2009). However, studies conducted in high income countries with organised screening programs reported that providing self-sampling kits to defaulters, particularly when in addition to a reminder letter, may improve their screening attendance (Gok, Heideman et al. 2010). All nonparticipants in organized cervical cancer screening in Espoo, Finland were randomized to receive a self-sampling kit (1,130 women) or a reminder letter (3,030 women) (Virtanen, Anttila et al. 2011). Participation rate in the self-sampling arm, 30%, was significantly higher than in the reminder letter arm, 26% (adjusted relative risk for participation= 1.13). Total participation in Espoo in 2008 rose significantly after the two interventions from 64.0 to 75.4%.

A randomized controlled study compared screening uptake rates between 4 different approaches (Giorgi Rossi, Marsili et al. 2011). In defaulters aged 35–64 years two control groups received standard recall letters to perform either a Pap-test (first group) or a HPV test (second group) at the clinic, a third arm was sent letters offering a self-sampler for HPV testing, to be requested by phone; a fourth group was directly sent the self-samplers to their homes.

The screening uptake with standard recall was 13.9% (n=619). Offering HPV testing at the clinic had a non-significant effect on uptake (n=616, relative risk (RR) =1.08; 95% CI=0.82–1.41). A self-sampler on request had the poorest compliance, 8.7% (n=622, RR=0.62; 95% CI=0.45–0.86), whereas direct mailing of the self-sampler registered the highest compliance: 19.6% (n=616, RR=1.41; 95% CI=1.10–1.82). In a study of 369 women, 179 (49%) ordered a Qvintip self-sampling device, of whom 117 (32%) performed self-sampling at home and sent the sample to the laboratory for analysis (Stenvall, Wikstrom et al. 2007): a third of the samplers (35%) were not returned.

3. Reasons for non-participation in cervical screening programmes

Reasons for non-participation in cervical screening depend on many factors. They are largely dependent on the accessibility and robustness of the programme. Within a well-established cervical screening programme, the reasons for non-participation can be categorised into attitudinal and non-attitudinal, although they are often multi-factorial.

Factors that negatively affect cervical screening uptake have been categorised into 3 areas by Waller (Waller, Bartoszek et al. 2009).

a) Demographic factors such as age, marital status and ethnic group
b) Structural/ health-care factors such as appointment times, female practitioners and 'friendly treatment'
c) Attitudinal factors like embarrassment, trust and concerns about discomfort.

a. Demographic factors

Demographic factors often correlate with each other. Socio-demographic and attitudinal correlates of self-reported cervical screening uptake were investigated among 1307 women in the target age group who participated in two national surveys conducted in Britain (Sutton and Rutherford 2005). Uptake was highest among married and separated women and lowest among single and widowed women. The strong effects of car ownership and housing tenure showed a robust positive association with uptake.

In one study, ethnicity was the most important predictor for participation in cervical screening (Moser, Patnick et al. 2009); white British women were significantly more likely to have had a

cervical smear than were women of other ethnicity with odds ratio 2.20, (95% CI: 1.41-3.42). Uptake of cervical screening was greater among more educated women but was not significantly associated with cars, housing tenure, or region.

In a population based survey in Britain examining socio-demographic predictors of HPV testing and vaccination acceptability, (Marlow, Waller et al. 2008), the screening attendance was associated with education level (odds ratio [OR] = 1.66, confidence interval [95% CI]: 1.07-2.56) and being married (OR = 2.04, 95% CI: 1.37-3.03).

b. Healthcare factors

A telephone-based questionnaire about future attendance at cervical cancer screening which included 400 defaulters in Sweden (Oscarsson, Wijma et al. 2008) assessed their requirements for attendance and potential ways of improving attendance. 120 considered having a cervical smear taken, and 50 of them wanted help to accomplish this. When meeting the women's requirements, such as being assured of friendly treatment and a suitable appointment time, the numbers of registered cervical smears were higher for the study group compared with a control group. Still, the most hard-to reach defaulters did not attend screening.

A postal questionnaire survey was used (Olowokure, Caswell et al. 2006) to compare preferred appointment times with those given for cervical screening. Although 33% of respondents received appointments between 10h00 and 11h55, only 17% wanted an appointment at that time. Nineteen per cent of respondents wanted appointments between 18h00 and 20h00, but only 4% received them. Saturday appointments for cervical screening are not given; however, overall approximately 13% of those surveyed would have preferred a Saturday appointment.

Women's lack of knowledge of cervical screening appears to be an important factor accounting for non-attendance at cervical screening (Neilson and Jones 1998). The response rate to this questionnaire- based survey conducted in Edinburgh was 72/187 (38%). The majority of women showed preference in a female professional taking the smear. Practical problems of time and venue were not considered insurmountable. The main reasons cited for non-compliance were the fear and dislike of the test itself. Although the majority of women felt the invitation to attend screening was clear and easy to understand, there was a lack of knowledge with regard to both the screening itself and the possible causes of cervical cancer.

c. Attitudinal factors

Attitudinal factors can be categorized into embarrassment, trust and concerns about discomfort.

Women who reported that their last test had been painful or embarrassing held more negative views of a future test, but a prior positive result was not implicated in women's expectations concerning future screening. Orbell and colleagues (Orbell 1996) interviewed 276 women who had recently undergone the cervical smear test concerning their screening experience, the screening test and their future screening expectations. Anticipated embarrassment and other negative attitudes towards screening for example, "There's no point going for screening if you don't have any symptoms" were significant independent negative predictors of uptake (Sutton and Rutherford 2005).

Lack of trust regarding healthcare professionals who collect the sample and/or the test itself is another attitudinal factor that affects screening attendance. A study (Blomberg, Ternestedt et al. 2008) was conducted to explore how women who actively declined participation in cervical screening in Sweden reasoned regarding their choice. Factors related to women's decisions not to participate in screening at all included a lack of confidence in the benefits of screening, a previous bad experience, a belief in one's own ability to pick up any changes or a belief that one was not at risk of cervical cancer, as well as a number of unconventional standpoints on social and political issues. Authors recommended the use of Jepson et al.'s ethical framework to peruse the evidence-base underlying women's 'informed decision-making' about CCS, which was suggested to be more constructive than discussing potential participants' knowledge versus lack of knowledge.

A study conducted by tape-recorded interviews of a sample of 14 women in southeast Sweden who had chosen not to attend CCS during the previous 5 years was analyzed by qualitative inductive content analysis. These women reported various degrees of lack of trust in health-care. ‘I do not need to’, ‘I do not want to’ and ‘I do not give it priority’ themes were recognized. The women had a positive attitude to screening but as long as they felt healthy, they chose not to attend. A negative body image, low self-esteem, feelings of discomfort and fear of the results also influenced their non-attendance.

Concerns about discomfort were other reasons for non-attendance. Four hundred Swedish women were randomized from a population based register (Oscarsson, Benzein et al. 2008), of

which 133 non-attendees answered the Cervical Screening Questionnaire in telephone interviews. Previous negative experience (feelings of discomfort with the gynecologic examination) was one of the top 3 reasons for non-attendance. Non-attendees who reported non-attendance due to experiences of discomfort associated with the gynecologic examination, estimated that they would experience great discomfort during their examination. A history of sexual abuse was reported by 16.5%. By contrast, discomfort was one of the many reasons for non-attendance in Britain (administrative failures, unavailability of a female screener, inconvenient clinic times, lack of awareness of the test's indications and benefits, considering oneself not to be at risk of developing cervical cancer, and fear of embarrassment, pain, or the detection of cancer) according to Fylan (Fylan 1998).

4. Different sampling methods

Over 16 different vaginal self-sampling devices could be found. Some self-collection devices attempted to simulate the gold standard cervical sampling technique to a certain extent. Therefore, a brief overview of the conventional and standard cervical sampling technique will be given first.

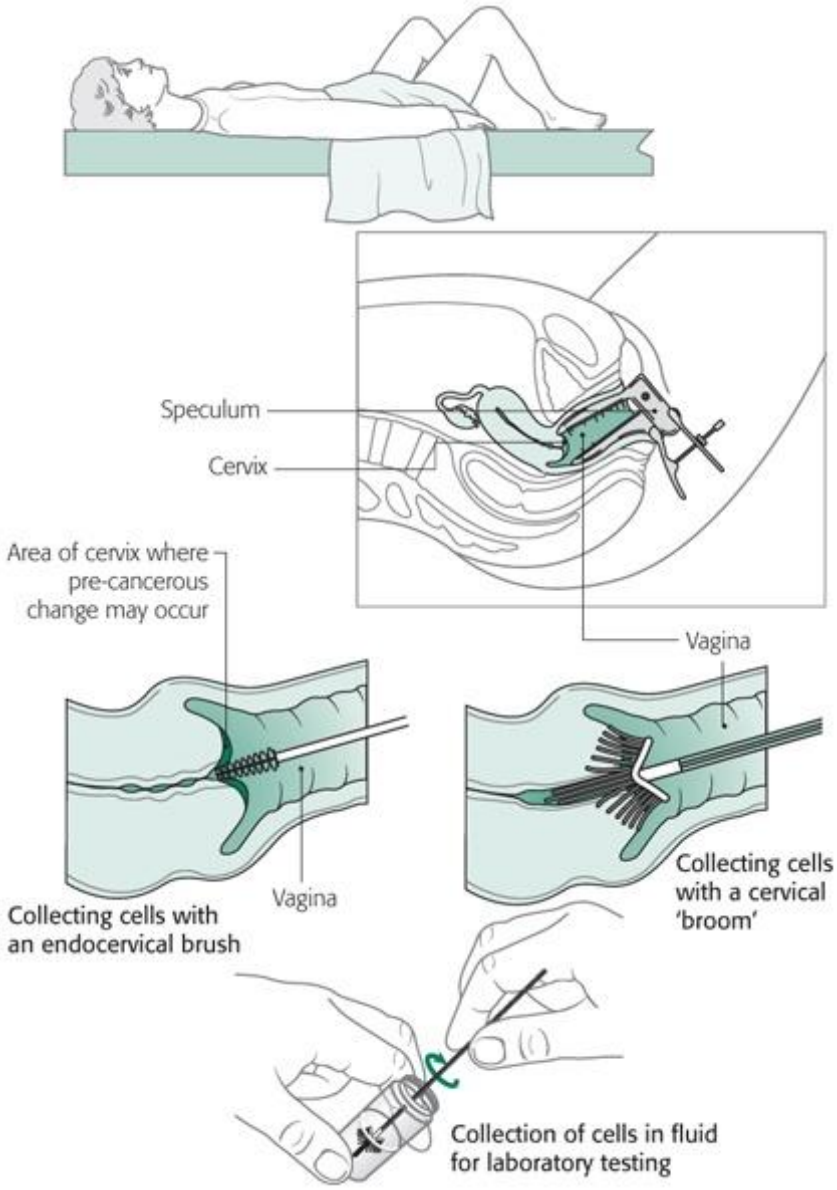
(a) The conventional cervical smear collection technique

The primary purpose of the conventional cervical smear technique is to make a Papanicolaou smear on a glass slide, to be examined under a light microscope by a pathologist. Although the sampling technique has been slightly evolved since it was first introduced by George Papanicolaou between 1928 and 1948 (Papanicolaou and Traut 1997), cytopathological principles which underpin the smear test remain unchanged.

(b) The standard cervical smear collection technique

The standard cervical screening sample in UK is liquid based cytology. The specimen is deposited in a 20mL preservative liquid. This is facilitated by collecting the cervical sample with brushes and brooms made out of plastic (Fig 1.2.3), a spatula can be used as an alternative.

Fig 1.2.3: Standard cervical sampling technique



(c) Self-collection devices

It is reasonable to assume the best self-sampler will be capable of collecting a cervical sample which is similar to the gold standard clinician collected sample. However, this may not be a realistic expectation, considering the complex mechanics involved in cervical cytology sample collection. A self-sampler which gets closer to the clinician's technique could be the best alternative to the gold standard.

Table 1.2.1: Comparison of different vaginal self-sampling devices

	Name	Type of device	Liquid transport medium needed	Potential strengths	Potential limitations
1	Qvintip	Modified flocked swab	No	Looks simple, sampling is easy	Detachment of the flocked tip may cause problems
2 & 3	1st gen. Delphi/ Pentarhei	Lavage	Yes	It looks like a syringe which may be user-friendly	Lavage may be perceived 'messy'
4	2nd gen. Delphi	Lavage	Yes	Relatively smaller, sampling is easy	Premature suction mechanism may yield a less cellular sample
5	Viba brush	Brush (100% plastic)	May be	Looks simple, sampling is easy, large surface area catches a large sample, inexpensive	Improper use could be painful
6	Viba brush+ FTA elute	Brush (100% plastic) with a fixative cartridge	No	Colour change of the cartridge may be reassuring to the woman	The whole sample may not be placed on the cartridge by the woman
7	Genipap	Brush with a short plastic sleeve	May be	The sample is 'protected' by the device sleeve	Sampling could be very difficult
8 & 9	QIAGEN/ Digene cervical brush	Brush (nylon bristles+ metal rod)	Yes	Looks simple, sampling is easy, large surface area and nylon bristles catch a good sample	Disposal of the metal rod of the brush can be difficult
10	Flocked/ Dacron swab	Vaginal swab	Yes	Looks very simple, sampling is very easy, inexpensive	The small surface area limits the volume of the sample
11	Cotton swab	Vaginal swab	No	Looks very simple, sampling is very easy, inexpensive	Cotton may inhibit HPV DNA detection
12	POI/NIH sampler	Modified flocked swab with a short sleeve	Yes	Sleeve enhances upper vaginal sampling	Sampling is complicated and could be difficult
13	Fournier	Modified, ejectable tampon	May be	Long sleeve enhances upper vaginal sampling	Tampon part could be inadvertently ejected inside the

		with a long plastic sleeve			vagina, sampling may be complicated
14	Pad	Sanitary Pad	No	Sampling is easy	Shipping and processing could be difficult
15	Tampon	Vaginal tampon	No	Sampling is easy for women who used to use tampons	May not be universally acceptable
16	Evalyn brush	Modified Viba brush with a short plastic sleeve	No	Sleeve enhances upper vaginal sampling, large surface area enhances volume of the sample	Appears large and complicated

(d) The main characteristics of an ideal self-collection device

It appears that development and improvement of self-sampling devices is still an ongoing process (Schmeink, Bekkers et al. 2011). The majority of the studies assessing self-sampling have used liquid based storage and transport media. The use of liquid based self-samples has the impractical consequence that fluids may leak, and special precautions have to be taken for transport. This potentially hampers the large scale introduction of cervico-vaginal self-sampling methods as the sampling kit must be suitable for posting. The use of dry transport methods may eliminate these disadvantages. Samples may be transported and stored using a 'dry' test tube. However, over-drying may reduce the number of HPV infected cells available for DNA testing.

Above all, the overall cost for sample collection should be cheaper.

Although self-sampling brushes with long, multiple bristles (Viba brush) collected cellular sample representative of the cervix (Yoshida, Sano et al. 2011), vaginal lavage samples are less able to do this. A self-sampling study which used the Delphi Screener (Jentschke, Lange et al. 2013) found that 27/140 (19%) physician-collected samples were p16 (INK4a) ELISA positive. In contrast, p16 (INK4a) ELISA was positive in only 1/140 (1%) of vaginal lavage samples.

Evidence suggests that 'wet' self-samplers have a better HPV yield than the 'dry' ones (Please refer to the table 2.2.1). HPV positive rates were 10.3-15.3% with the Delphi Screener whereas; it was 6.0-6.6 with Qvintip which appears to collect a good sample (Darlin, Borgfeldt et al. 2013). Issues in relation to the dryness could be rectified by not letting the sample dry out. Although the

time interval between sample collection and testing could be shortened, protecting the mucous sample from evaporation until it is placed in the liquid medium is the best way forward.

Collection of HPV infected cells from high in the vagina with no contamination from the lower vaginal flora is desirable for the specificity of the screening test. However, it can be argued that a test that will detect any hrHPV infection will have an excellent negative predictive value for cervical dysplasia. Intuitively, development of cervical dysplasia is less likely in a woman whose lower genital tract is free from hrHPV infection, than a woman who has no hrHPV in the cervix but when it is present in the vagina.

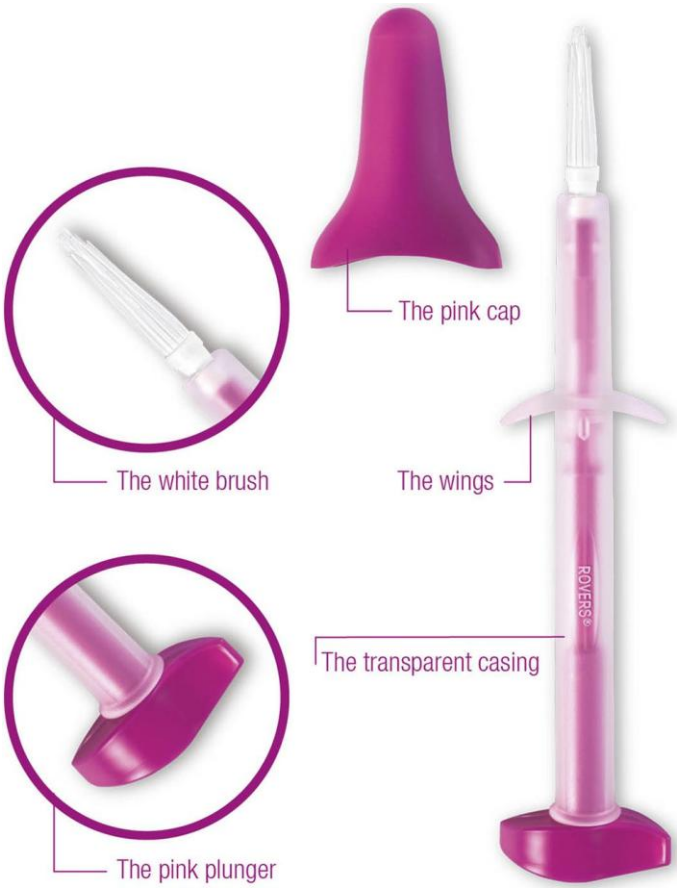
Most of these self-sampling studies were small and non-population based. Large scale-community based studies have been carried out more recently in the Netherlands (Gok, Heideman et al. 2010), China (Belinson, Du et al. 2011) and Mexico (Lazcano-Ponce, Lorincz et al. 2011). Swab based devices have been used in most of these studies except in 2: the Delphi Screener and Viba brush. This can be a main confounding factor between these studies as the HPV positivity largely depends on the quality of the sample that is being collected.

Most self-sampling studies used different sampling devices for self-collection and clinician collection, which could affect the number of HPV infected cells sampled. This should affect the HPV result, its sensitivity and concordance. By contrast, a study conducted in Taiwan (Chang, Tseng et al. 2002) used the same sampling device (cotton swab) for self as well as clinician sampling. A total of 1194 women were prospectively registered from 1997 to 1999. A vaginal swab was self-collected 3 days before a physician collected a cervical swab. Samples were analyzed using HC 2 assay. Among them, 144 (12%) of self-test samples and 155 (13%) of physician-obtained samples were hrHPV positive. No significant differences were observed in the screening rate for cervical cancer using either the self-collected samples or the physician-collected samples. The sensitivity of cervical pre-cancer or cancer detection using self-obtained HPV testing was higher (96.3%) as compared with the Pap smear (79.2%) ($p< 0.02$). There is no doubt that a cervical swab is not the best cervical sampler for cytology screening. It is unlikely to be the best sampler even for HPV screening. Using sub-standard devices cannot be justified for screening purposes. However, this study suggested that if the same sampler was used to collect both cervical and vaginal samples, both samples could be equally good for HPV screening.

Evalyn brush

The Evalyn brush which is made of plastic was manufactured in 2011. The head of the Evalyn brush is identical to Rovers Viba brush (Fig 1.2.4).

Fig 1.2.4: Evalyn brush self-sampling device



Fifty women in Japan self-collected a vaginal sample with the Viba brush, one month after a clinician collected sample (Yoshida, Sano et al. 2011). LBC identified high-grade squamous intraepithelial lesions in 11 (22%) and 7 (14%) patients, low-grade squamous intraepithelial lesions in 19 (38%) and 16 (32%), atypical squamous cells of undetermined significance in 2 (4%) and 0 patients, in clinician collected and self-collected samples, respectively. A total of 37/50 (74%) of clinician collected and 41/50 (82%) of self-collected cases were positive for HPV, indicating that the Evalyn brush head should be able to collect a rich cellular sample for HPV screening.

The Evalyn brush is made of plastic. Its sleeve bypasses the lower half of the vagina, simulating the speculum of the standard cervical smear technique. The design of the sleeve aids easy insertion which should not cause any pain. The Evalyn brush is capable of collecting a rich cellular sample from the higher vagina, possibly from the ectocervix from its 3 cm long 14 flat bristles made of firm plastic. It is easy to use. It creates clicking sounds when the bristles are fully extended in the vagina as well as after each rotation. The manufacturer advises that it should be rotated five times, which is keeping in line with the cervical sampling technique. Its safety cap prevents the sample from drying out. Its plastic housing prevents accidental extensions of bristles. All of these eventually go inside a self-seal, tough plastic bag which protects the sample from drying as it prevents leakage of humidity/ moisture from the sample container. Hence, almost all samples that we received arrived in a near new condition. They were moist and appeared cellular when dissolved in the PreservCyt medium.

The Evalyn device together with the sample collected is sent to the laboratory so that the woman doesn't have to move the sample from the device to another container. Self-collection with the *Evalyn*® brush has shown a high level of concordance of 86% (kappa 0.72) with the clinician-collected sample for HPV testing and a good acceptability in 134 participants (van Baars, Bosgraaf et al. 2012).

In my opinion, some limitations of the Evalyn brush are that the sleeve is a little short, only 4.5 cm in length and the size of the cap is large 2.3 cm in width. The length of the vagina is 6-11 cm. If the length of the sleeve was another 2 cm long, it would overcome this problem, although bristles touching the cervix can cause some discomfort to some women. A large cap can be intimidating to some women. Moreover, a smaller size would make postage much cheaper. A small pen clip like cap would overcome this issue.

CHAPTER 2

Aims, objectives and study design

2.1. AIMS & OBJECTIVES

Aims

1. To explore potential methods of increasing cervical screening coverage.
2. To explore reasons for defaulting.

Primary objectives

1. To examine the screening attendance to see if it could be improved by offering more flexible smear (cervical cytology) options to defaulters.
2. To examine the screening attendance to see if it could be improved by offering self-sampling to defaulters older than 30 years.
3. To explore barriers to cervical screening and to find out what is acceptable to this cohort of defaulters.

Primary endpoints

1. A woman declinnig participation in the study
2. A woman accepting a screening test
3. No response after the screening reminder letter
4. No attendance at the second appointment at the hospital smear clinic

Secondary endpoints

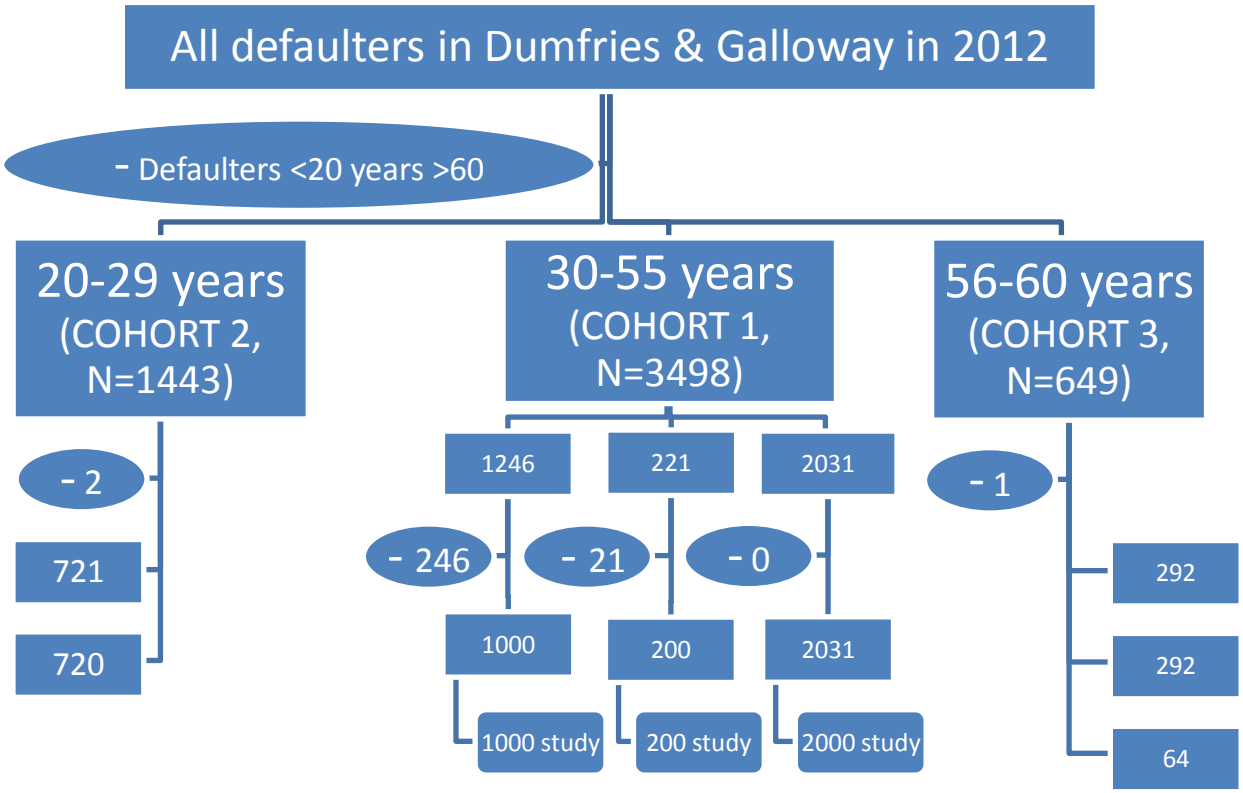
1. An HPV+ woman with a cytological abnormality referred to colposcopy
2. An HPV+ woman with normal cytology attending at the annual follow-up visit
3. No attendance at the second appointment at the annual follow-up clinic

2.2. STUDY DESIGN

According to the Dumfries & Galloway Cervical Screening 2012 Annual Report (based on the statistics on 01/01/2012), there were 6106 defaulters out of 36,903 screening eligible population in the Health Board. The total population of the Health Board was approximately 151,000.

Although we were aiming to include the whole population of defaulters into various research studies, defaulters outwith the normal screening age group were excluded. Remaining defaulters were recruited to different studies as per the following flow chart (Fig 2.2.1).

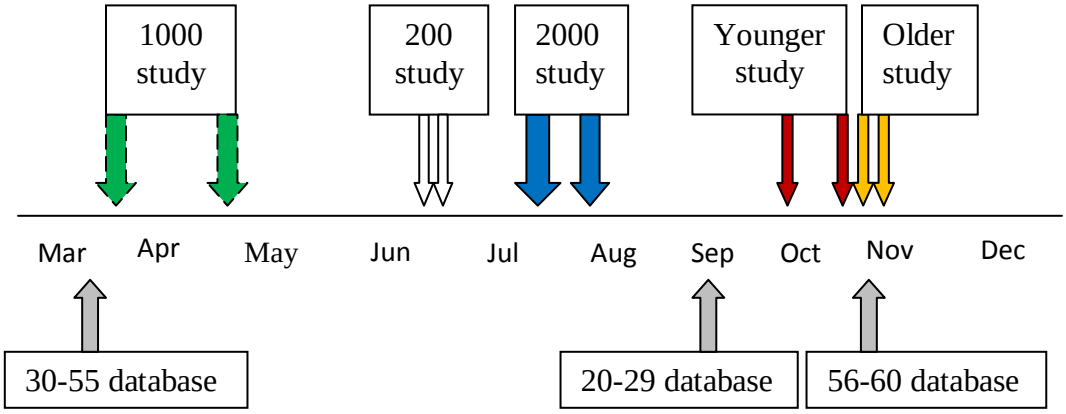
Fig 2.2.1: Main study design



Key: numbers within boxes represent number of women belonging to each category.

Recruitment of above 5 studies took place during following time periods in 2012: 1= 15 March-20 April; 2=18-22 June; 3=9-13 July; 4=3 Sep-29 Oct; 5=29-31 Oct (please see Fig 2.2.2).

Fig 2.2.2: Recruitment plan



The first taget of our studies was the 30-55 year old defaulters (cohort 1). They were recruited into 3 different studies (1000, 200 and 2000). Cohort 2 was recruited next, followed by cohort 3. Research conducted in each of these 3 main age groups will be presented separately as slightly different methodologies were tested in each. These are the main five intervenational studies. Some smaller studies carried out along with these main studies are described seperately to improve clarity.

The main reason why we had to 'space out' the study population was to accommodate screening positives smoothly to colposcopy without breaching waiting time standards. Other reasons were mainly logistical. The PI had to do numerous tasks during this period apart from recruitment.

The first database was generated in early March 2012. This included 3498 defaulters. The second database included 1441 defaulters aged between 20 and 29 years. This was received in early September (cohort 2- younger defaulter study). The third database included 565 defaulters aged between 56 and 60 years. This was received at the end of October 2012 (cohort 3- older defaulter study). All defaulters belonging to the whole screening population in Dumfries and Galloway were included in the above 3 databases.

The data were extracted using BOXI (Business Objects Interrogation Tool) associated with the SCCRS data by the Screening Services Manager, NHS Dumfries and Galloway. The data extracted were copied to an Excel spreadsheet which was sent to the Research and Development Department ordered by CHI number. It is known that the CHI number is not related to name, date of birth or address. Samples of this Excel spreadsheet were carefully examined by the Data Manager of the Research and Development Department and two main investigators. It appeared that any given large sample of it represented a full spectrum of age distribution of the 30-55 year old cohort. Hence, it was decided to allocate the first 1000 (1246-246 excluded) CHI numbers to the first study (1000 defaulter study), the second 200 (221-21 excluded) would be assigned to the second study (200 defaulter study) and the remaining 2031 to the final study ('2000' defaulter study) using this Excel sheet. The analysis of the age distribution of each cohort will be presented under each study.

CHAPTER 3

Validation studies and research methodology

VALIDATION STUDIES

3.1 Can women self-collect an adequate sample for HPV screening?

Study question

Can women self-collect an adequate sample with the Evalyn brush for Hologic Cervista HPV-HR testing?

Summary answer

All 14 vaginal samples were positive for genomic human DNA, which is deemed adequate samples. Some vaginal samples deposited in a larger volume of ThinPrep were falsely negative, probably due to dilution effect.

What is known and what this study adds

Women can self-collect adequate vaginal samples for HPV screening. But no previous study has used the Evalyn brush as a 'dry' self-sampler. Performance of the Hologic Cervista HPV-HR test with such an Evalyn sample was not known. Results of this study suggest that women could self-collect an adequate sample with the Evalyn brush for Hologic Cervista HPV testing. It appears that increasing the ThinPrep sample concentration reduces false negative results. Based on these results, a sample concentration method was adapted.

Limitations

Samples were collected from 7 subjects only; a larger number would have increased the validity of this study. Quantification of HPV DNA and co-testing of samples with a reference HPV test would have been useful.

Background

We wanted to demonstrate concordance between the clinician and self-collected samples regarding levels of gDNA (genomic human DNA) internal control within the *Hologic Cervista*® HR assay as well as the HPV DNA. In turn this will allow us to determine the suitability of the off-label assay for a self-sampling study.

Methods

A prospective, ethics approved study at Dumfries & Galloway Royal Infirmary's colposcopy clinic between 23/09/2011 and 07/10/2011. Patients who were eligible for the study were identified by going through the clinic list and clinical records. The sample size was aimed at between 5 and 10 as this was a proof of concept study, mainly to see if the Evalyn brush could collect a sample that would pass the internal control of the Cervista test.

Eligible patients were approached by the colposcopy nurse who briefly explained the study and they were provided with participant's information leaflet. Subsequently, patient consent was obtained. Women who consented to take part in the study were provided with two sterile *Rovers Evalyn*® brushes, along with verbal and written instructions for a sample collection. Women self-collected two samples with pre-labelled *Evalyn*® brushes in the bathroom next to the colposcopy clinic, immediately before they were seen. A standard cervical smear was obtained by the colposcopist before the colposcopy examination, using a *Cervex*® brush into a pre-labelled 20mL *ThinPrep*® vial. This was used as the HPV reference test material.

Evalyn® brushes with self-collected material were kept in the specimen package at room temperature (mimicking the postage time) at least for 48h (range 48-50 hours). The head of the *Evalyn*® brush was pulled out by a new, clean pair of disposable, plastic tweezers provided by the manufacturer and was put into a pre-labelled *ThinPrep*® vial before the cap was shut. Each pair of *Evalyn*® brushes were put into two different vials (one brush head per vial). One vial of *ThinPrep*® contained the standard volume of 20mL whilst other contained 5 mL. The sample was vortexed and the brush head was removed from *ThinPrep*® vial by a new, clean pair of tweezers. These *ThinPrep*® vials were kept at room temperature until they were despatched to the Scottish HPV Reference Laboratory (SHPVRL) in Edinburgh on 31st October 2011. Samples were subsequently tested for gDNA and HPV DNA with the *Cervista*® HR-HPV assay.

Results

The *Cervista*® HR-HPV assay has an internal control which detects genomic human histone DNA (gDNA) in the sample. It would not give a valid HPV result without passing the internal control. Please find results of the internal control (gDNA) in Table 3.1.1 and hrHPV DNA results in Table 3.1.2. Relevant history which includes the most recent cytology result and the diagnosis is recorded in the second column (diagnosis). The order that the self-taken vaginal sample was collected (first or second) is in the brackets in the last two columns.

All 10 Evalyn samples passed the internal control. All but one of the cervical samples passed the internal control. A woman who had been referred to the colposcopy clinic with post-coital bleeding with a recent normal smear had passed the internal control of self-collected samples, but failed in the cervical sample.

Table 3.1.1: Genomic human histone DNA results of the proof of concept study

Patient	Diagnosis	Smear for gDNA	Self-collected*	Self-collected*
			5mL *ThinPrep®* *gDNA*	20mL *ThinPrep®* *gDNA*
1	Moderate dysk- CIN3	Pass	Pass [2]	Pass [1]
2	Post-coital bleeding- smear negative 2 years ago	Fail	Pass [1]	Pass [2]
3	Previous CIN3- smear negative	Pass	Pass [1]	Pass [2]
4	Previous CIN1- current CIN3	Pass	Pass [2]	Pass [1]
5	Severe dysk- CIN2	Pass	Pass [2]	Pass [1]
6	Previous CIN1- biopsy normal	Pass	Pass [1]	Pass [2]
7	Previous adenocarcinoma- smear unsatisfactory	Pass	Pass [2]	Pass [1]

Table 3.1.2: HPV DNA results of the proof of concept study

Patient	Diagnosis	Smear for HPV	Self-collected*	Self-collected*
			5mL *ThinPrep®*	20mL *ThinPrep®*
1	Moderate dysk- CIN3	Positive	Positive [2]	Positive [1]
2	Post-coital bleeding- no smear	Negative	Negative [1]	Negative [2]
3	Previous CIN3- smear negative	Negative	Negative [1]	Negative [2]
4	Previous CIN1- current CIN3	Positive	Positive [2]	Negative [1]
5	Severe dysk- CIN2	Positive	Positive [2]	Negative [1]
6	Previous CIN1- biopsy normal	Negative	Negative [1]	Negative [2]
7	Previous adeno ca-smear unsatis	Negative	Negative [2]	Negative [1]

*[1]=first sample; *[2]=second sample; Pass = sufficient gDNA; Fail= insufficient gDNA

hr-HPV was positive in 3/7 cervical samples. All 3 cervical HPV positive samples had current hgCIN. HPV results of vaginal samples which were deposited in 5mL ThinPrep matched the cervical counterparts. The Evalyn sample which was deposited in 20mL of ThinPrep was collected by the woman who was referred with severe dyskaryosis had a negative HPV result. All other vaginal samples in 20mL ThinPrep had the same result as in the cervical counterpoint

Discussion

All self-collected vaginal samples contained an adequate amount of genomic DNA, indicating that samples were cellular enough for the internal control of the Cervista test to give us a valid result. The test cannot differentiate cervical cells from other types. However, this is unlikely to cause any issue, as exfoliated abnormal cervical cells have been found in adequate amounts in self-collected samples in other studies (Yoshida, Sano et al. 2011; Yoshida, Sano et al. 2011; Jones, Mansukhani et al. 2013) when the Viba brush and sampler have been used. The brush head of the Viba brush and the Evalyn brush are virtually identical as they are manufactured by Rovers Medical Devices, The Netherlands. Moreover, vaginal self-sampling for HPV testing is known to collect a sample which is similar to the cervical counterpart. However, it is best practice to 'test drive' the methodology before it is used in mass scale.

Conclusions

Self-collected vaginal samples in 5ml or 20ml of collection fluid with the *Evalyn*® brush showed an excellent agreement with their cervical counterparts for adequacy of the sample as defined by genomic DNA. However, two samples placed in 20mL vials were falsely negative despite being collected first by the woman, suggesting that the HPV DNA concentration plays an important role. Based on this proof of concept study results, industry experts suggested concentrating the ThinPrep sample before DNA extraction. After senior level discussion between the Hologic Limited and the SHPVRL, the following approach was adapted to process ThinPrep samples for our study.

Method of sample concentration

1. The whole 20mL PrecervCyt sample is transferred from the ThinPrep pot to a 50mL Falcon tube.
2. It is then centrifuged at 1,110g for 10 min to pellet the cells.
3. All but 5 mL of the PreservCyt solution is removed and the cells are re-suspended in the remaining 5mL of solution before being returned to the original ThinPrep pot

3.2 The storage study

Study question

How long will 'dry' Evalyn samples remain viable for HPV screening?

Summary answer

It appears that a vaginal sample self-collected with the 'dry' Evalyn® brush remains viable for HPV testing for 2 weeks when a PCR based test is used for testing.

What is known and what this study adds

Performance of the Evalyn brush as a 'dry' self-sampling device was unknown. It appears that a vaginal sample self-collected with the 'dry' Evalyn® brush remains viable for HPV testing for 2 weeks when a PCR based test is used for testing. There is a good agreement between the clinician-collected cervical sample and self-collected vaginal sample for HPV screening in subjects with hgCIN.

Limitations

Samples were collected from 10 subjects only; a larger number would have increased the validity of this study. It would be impossible to divide the Evalyn sample into 2 identical portions by cutting the brush head into 2 halves. This process increases the risk of contamination and loss of sample. Ideally, half of the sample should have been suspended in half of ThinPrep volume (10mL rather than 20mL).

Background

The Evalyn brush is a dry sampling device which does not require liquid/alcohol based medium for specimen transportation. This makes a considerable difference to the transportation cost as alcohol based media cannot be posted. Although non-alcohol based transport media can be sent in the post, it can cost about £5.60 (Royal Mail Special Delivery 2012), whereas postage for the dry Evelyn brush costs only £0.10 (RoyalMail pre-paid First Class 2012). Cost-effectiveness plays the biggest role when choosing a good screening tool. If the dry Evalyn sample sent through the post is as good as the gold standard sample for HPV screening, the cheaper option can be adapted.

Methods

Ten women attending at the colposcopy clinic with an abnormal cervical cytology test were asked to self-collect a vaginal sample with the Evalyn® device, in the patients' toilet in the clinic. A cervical smear was taken with a Cervex® brush, as usual, just before the colposcopy examination.

The Evalyn® brush kit was sealed in its plastic bag and was kept in a cardboard box at room temperature, simulating a postal sample. The temperature of the room was recorded daily, both day and night. Temperatures recorded (n=8) were between 20ºC and 21 ºC. On day 7, the distal half (tip) of the Evalyn® brush head was cut into ThinPrep® 20mL vial with a sterile pair of scissors, vortexed for 2 minutes and the bristles were removed using a sterile pair of plastic tweezers. Utmost care was taken to prevent potential contamination. The Evalyn® device was stored again as explained before. The remaining sample was deposited in ThinPrep® 20mL on day 14.

Seventeen samples of 3mL of each ThinPrep® pot were tested with Cobas® 4800 test first. The remaining 13 were run subsequently. We had to use a qPCR test for this study. Roche Cobas 4800 is a qPCR based test for simultaneous detection of 14 high-risk HPV types that can be used to specifically identify HPV16 and HPV18 DNA

Results

Women from 3 consecutive colposcopy clinics were recruited to participate in this study. Ten women consented to take part in the study. They were aged from 23 to 38 years. Half of the women had high grade smear abnormality. The colposcopy diagnosis was a high grade CIN in all but one. Histology confirmed colposcopy diagnosis in all except one case of CIN1 of which the colposcopy diagnosis was high-grade CIN. Please see the results summary in table 3.2.1.

All ten cervical samples tested positive for hrHPV on Cobas. HPV 16 was found in 7 samples and HPV (other) were found in 7 samples; six samples had both HPV16 and another high risk HPV types HPV (other).

Table 3.2.1: Storage study results

No	Age	Smear	Colpo	Histo/ Specimen	Cx HPV 0wk	Cx CT 0wk	Vag HPV 1wk	Vag CT 1wk	Vag HPV 2wk	Vag CT 2wk
1	24	Sev	hgCIN	CIN3 LLETZ	16 Other	24.7 24.6	16 Other	29.1 29.2	16 Other	32.4 35.5
2	23	Mod	hgCIN	CIN3 LLETZ	16 Other	27.6 27.4	16 Other	32.8 36.5	16 Other	31.8 35.9
3	27	Mild x2	lgCIN	CIN1 Punch Bx	16 Other	26.8 29.8	16 Other	31.3 33.7	16 Other	29.8 34.3
4	36	Mild+ bnc	hgCIN	CIN2 LLETZ	Other	31.3	Other	38.4	Other	39.0
5	38	Sev	hgCIN	CIN2 LLETZ	Other	28.5	Other	35.4	Other	37.9
6	36	Mod	hgCIN	CIN2 LLETZ	16	25.3	16	27.3	16	27.3
7	31	Mild+ bnc	hgCIN	CIN3 LLETZ	Other	31.1	Other	33.6	Other	37.1
8	30	Mild+ referr al	hgCIN	CIN3 LLETZ	16 Other	25.8 26.3	16 Other	30.6 28.7	16 Other	32.2 31.0
9	24	Mod	hgCIN	CIN2 LLETZ	16	24.3	16	30.5	16	34.0
10	28	Mild+ bnc	hgCIN	CIN1 LLETZ	16	38.3	Neg		Neg	

CT= cycle threshold, 16=HPV 16, other= a high-risk HPV type other than HPV 16.

The CT value of the patient number 10 has been excluded from the analysis as it did not have any CT values for the vaginal sample. All other 13 sets of CT values were analysed using a linear regression model with the difference in cycle numbers as the outcome, and allow for clustering (so the standard errors are calculated using a clustered sandwich estimator). There is a significant difference between the cycle numbers needed for cervical week-0 and vaginal week-1 (Fig 3.2.1.a). There is a significant difference between the cycle numbers needed for cervical week-0 and vaginal week-2 (Fig 3.2.1.b). There is not a significant difference between the cycle numbers needed for vaginal week-1 and vaginal week-2 (Fig 3.2.1.c).

Fig 3.2.1: Analysis of the storage study data

(a) diff1= cervical ct at 0 week - vaginal ct at 1 week

```
. reg diff1, cluster(no)

Linear regression                                       Number of obs =      13
                                                        F(  0,     8) =    0.00
                                                        Prob > F      =       .
                                                        R-squared     =  0.0000
                                                        Root MSE      =  2.0451

                                    (Std. Err. adjusted for 9 clusters in no)
------------------------------------------------------------------------------
             |               Robust
       diff1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |  -4.892308   .6012474    -8.14   0.000    -6.278787   -3.505829
------------------------------------------------------------------------------
```

(b) diff2= cervical ct at 0 week - vaginal ct at 2 weeks

```
. reg diff2, cluster(no)

Linear regression                                       Number of obs =      13
                                                        F(  0,     8) =    0.00
                                                        Prob > F      =       .
                                                        R-squared     =  0.0000
                                                        Root MSE      =  2.7413

                                    (Std. Err. adjusted for 9 clusters in no)
------------------------------------------------------------------------------
             |               Robust
       diff2 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |  -6.515385   .8398678    -7.76   0.000    -8.452124   -4.578646
------------------------------------------------------------------------------
```

(c) diff3= vaginal ct at1week - vaginal ct at 2 weeks

```
. reg diff3, cluster(no)

Linear regression                                       Number of obs =      13
                                                        F(  0,     8) =    0.00
                                                        Prob > F      =       .
                                                        R-squared     =  0.0000
                                                        Root MSE      =  2.2223

                                    (Std. Err. adjusted for 9 clusters in no)
------------------------------------------------------------------------------
             |               Robust
       diff3 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |  -1.623077    .786693    -2.06   0.073    -3.437194    .1910406
------------------------------------------------------------------------------
```

Discussion

Vaginal samples self-collected with the 'dry' Evalyn® brush remain viable for HPV testing for 2 weeks. In a real time PCR (qPCR) assay a positive reaction is detected by an accumulation of a fluorescent signal. The CT (cycle threshold) is defined as the number of cycles required for the fluorescent signal to cross the threshold (i.e. exceeds background level). CT levels are inversely proportional related to the amount of target nucleic acid in the sample (i.e. the lower the CT level the greater the amount of target nucleic acid in the sample). CTs less than 29 are strong positive reactions indicative of a good quantity of target nucleic acid in the sample. CTs between 30 and 37 are positive reactions indicative of moderate amounts of target nucleic acid. CTs between 38 and 40 are weak reactions indicative of minimal amounts of target nucleic acid which could represent an infection state or environmental contamination (manufacturer's information).

CT values of this PCR test suggest that there is a slight reduction of the viral load between weeks 1 and 2, which is unlikely have any clinical significance, as most of our main study samples were received within 2 days of collection. There is a good concordance between the clinician versus the self-collected samples. Only one discordant sample, participant 10- CIN1 had the lowest cervical viral load (CT=38.3) and the vaginal samples were negative. We used only 3mL out of 20mL in the ThinPrep vial for this PCR assy. No sample concentration step was involved. CT values would have been lower, if the method of sample concentration (please see study 2.1) of the whole sample had been used. On the other hand, CIN1 has nearly 70% chance of regression. This false negative result would probably not cause significant harm.

There is a perfect concordance (in terms of HPV positivity) between the cervical and vaginal samples in high grade CIN (all except sample number 3 and 10). A study which investigated the use of quantitative real-time PCR (QRT-PCR) which is a detection method that is considered to be more sensitive than conventional PCR (Seth, Rippin et al. 2005), measured the viral load (copies/ µg DNA) in cervical, vaginal and urine samples grouped according to histological classification. The highest viral load was reported in cervical followed by vaginal (Table 3.2.2) and urine samples (Daponte, Tsezou et al. 2008).

Table 3.2.2: Viral load in different samples

	Minimum	Median	Maximum
A. Viral load—cervix (p <0.001)			
Low grade (n = 49)	2 245	26 366	6 994 554
High grade (n = 36)	3 077	1 236 781	9 182 746
Cancer (n = 15)	94 110	7 793 442	7 558 141
B. Viral load—vagina (p <0.003)			
Low grade (n = 49)	0	16 653	984 650
High grade (n = 36)	0	20 503	984 650
Cancer (n = 15)	13 302	78 835	838 045

The CT value of the half of the Evalyn sample is less than the cervical counterpart. It would be interesting to know the quantity of HPV (CT values), between the cervical sample and the complete Evalyn sample (not half of it). However, using 2 separate Evalyn samples may not be ideal for this purpose as the second sample may not catch a cellular sample as well as the first. Although cutting may not divide the sample precisely into 2, it would probably be the better of two options. This limitation of half of the Evalyn sample may have been overcome if the ThinPrep sample had been appropriately diluted. For example, the cervical sample could have been diluted x 2 by adding another volume (20mL) of ThinPrep to the smear that had been collected. Another study looking at the CT value of the whole of the Evalyn sample in a more realistic sample (e.g. a sample stored only for 2-3 days) versus its cervical counterpart would also be interesting.

The quantification of HPV DNA in self collected vaginal samples has been researched evaluating other self-sampling devices. Similar HPV positive rates between the cervix (13%) and the vagina (12%) have been reported in a large study (N=1194) when the same type of sampler (Dacron swab) has been used by clinician and for self-collection.

The viral load in a self-collected sample was lower than but comparable to that of the gold standard cervical sample; even though the self-collected vaginal sample was stored for 1 to 2 weeks before testing. These findings would encourage the use of the ‘dry’ Evalyn device for HPV screening. We had to limit the number of participants to 10 due to resource limitations. A study with the adequate power to calculate concordance between cervical and self-collected

vaginal samples and dilution of cervical sample twice to be comparable with the half of the Evalyn sample might have strengthened our findings.

Conclusions

It appears that a vaginal sample self-collected with the 'dry' Evalyn® brush remains viable for HPV testing for 2 weeks when a PCR based test is used for testing. There is a good agreement between the clinician-collected cervical sample and self-collected vaginal sample for HPV screening in subjects with hgCIN.

3.3 How accurate are the addresses found in the Scottish Cervical Call-Recall System (SCCRS)?

Study question

How accurate are the addresses found in the SCCRS?

Summary answer

Addresses in the SCCRS are more inaccurate than the Sci Store Live database (OR=3.4, 2.3-5.0).

What is known and what this study adds

Inaccurate addresses in the screening database may adversely affect screening participation. There is no published evidence comparing accuracy of addresses found in the SCCRS. The odds ratio of an address being wrong in SCCRS relative to Sci Store Live database is 3.4 (2.3-5.0). Our data suggest that about 8% of screening letters sent by SCCRS may not reach the target, which can be improved.

Limitations

This study assumed that letters which were not returned undelivered were received by the appropriate person. This is not entirely correct as the person may no longer living in that address and the mail redirection service could be inactive. Some letters may be lost even after it was delivered to the right place. Some people may not read the (screening) letter even if it was received safely. Addresses on two databases were cross-checked twice, once on the computer, once on the hard copy. But, there is still a room for human error of not recognising the mismatch.

Background

No screening database appears to be perfect. A total of 398 (10%) ineligible women, because of incorrect addresses or previous hysterectomies were identified in the self-sampling study which was conducted in Sweden by Lindell and colleagues (Lindell, Sanner et al. 2012). Around 20% addresses in the cervical screening database in London was predicted to be inaccurate or 'ghosts' (letters sent to an inaccurate addresses) by the Szarewski self-sampling study group

(Szarewski, Cadman et al. 2011). Inaccurate addresses could be more common among women who were categorised as screening programme defaulters. We attempted to evaluate this situation in a cervical screening defaulter database in rural Britain (Dumfries and Galloway).

Each participant's SCCRS address in the 1000 and the study groups were double checked by the Research and Development Support Unit at NHS Dumfries and Galloway against the TOPAS patient access database, which is believed to be more up-to-date. This revealed some inaccuracies of SCCRS addresses, in comparison to the TOPAS. Consequently, a total of 246 (246/1246=19.7%) addresses that did not tally were removed from the 1000 study group, and 21(21/221=9.5) were removed from the 200 study group. Still, some letters have been returned undelivered. One letter was sent to a lady who had passed away, sometime before. This unpredicted situation led us to investigate the accuracy of addresses found in the SCCRS database.

We aimed to find the most accurate address for our younger (<30 years old) defaulters study where different smear options were offered. We came to know that the Sci Store Live database has the most up-to-date addresses of the public/ patients. The Sci Store Live database is a national patient access database which is maintained by an organisation in partnership with the NHS Scotland. We decided to cross check SCCRS addresses of the younger defaulter study group against the Sci Store Live database.

Methods

Cervical Screening Programme defaulters aged between 20 and 29 years living in Dumfries & Galloway were identified in August 2012. There were 1441 defaulters. We checked all of these 1441 SCCRS addresses on the Sci Store Live database from 2nd to 6th day after pulling the data out of SCCRS to create the research database. Addresses were cross-checked twice by the PI.

Addresses that did not match (n=82) were identified. On the 8th day, a non-selected sample of 10 discrepant addresses (every 8th address) was chosen to confirm their accuracy. Ten phone calls were made to the GP of the patient through the hospital switch board to find the correct address. Seven different GP practises were contacted. The address that the GP held was checked against the address on the database.

We could not find a reliable way of finding the accurate address of these 82 defaulters. This pushed us to hold on to those addresses for 2 months. These 82 addresses on the database were checked against the Sci Store Live database as well as on the SCCRS database in the 9th week.

There is a tab called 'timeline' both in SCCRS as well as Sci Store Live. It shows the date and the time that the person's address had been changed. The Sci Store Live has further details on this which includes the time and venue that the address has been updated. The timeline of the address changes were compared in these 2 databases.

Results

Of 1,441 addresses 1,359 (94%) matched. A total of 1,359 letters were sent to relevant addresses. Thirty four (2%) letters were returned undelivered.

Eighty two addresses did not match. A sample of 10 discrepant addresses was selected. Every eighth address of the unmatched address was chosen (numbers 8 16, 24, 32, 40, 48, 56, 64, 71 and 80). Ten phone calls were made to the GP of the patient though the hospital switch board to find the correct address. Seven different GP practises were called. It appeared that the GP had the same address as per SCCRS, except in one case.

On week 9, 67 out of 82 addresses matched between the SCCRs and the Sci Store Live database. All 82 letters were posted to the address found on the Sci Store Live database. Three letters were returned undelivered.

Correlation of the timeline indicated that the Sci Store Live database is more up-to-date than the SCCRS database.

Despite being deemed as accurate by 2 databases, 2.6% (34+3)/1441 letters were returned undelivered in this cohort of younger (20-30 years old) defaulters. This indicates that no database is perfect and 2.6% addresses in the Sci Store Live could be inaccurate. About 8% (119/1441) addresses in the SCCRS could have been inaccurate. The odds ratio of SCCRS addresses could be inaccurate in comparison to Sci Store Live is 3.42 (2.3-5.0).

Discussion

The Sci Store Live database has the more up-to-date addresses than the SCCRS. The Sci Store Live is expected to have more accurate addresses as it is a 'live' database. Six percent (1,359/1441) of address in the SCCRS did not match with the Sci Store Live. Despite agreement by 2 databases, up to 2% of letters were returned undelivered in this cohort of 20-30 years old defaulters.

These data also suggest that about 8% of screening invitation letters sent by SCCRS may not reach the targeted women. However, such women will probably receive the reminder letter which will be sent 2-9 months after the first invitation (prompt letter).

Conclusions

The Sci Store Live database has more up-to-date addresses than the SCCRS. The odds ratio of SCCRS addresses could be inaccurate in comparison to Sci Store Live is 3.42 (2.3-5.0). This indicates that about 8% of screening letters sent by SCCRS may not reach the target.

3.4 RESEARCH METHODS

Ethical, Caldecott and management approval

The West of Scotland Research Ethics Service approved this study on 7 October 2011 (Reference No: 11/AL/0333). Please find the main ethical approval and two amendments in the Appendix 4. The Caldecott Guardian of NHS Dumfries & Galloway approved the access to the Scottish Cervical Call-Recall System database on 12 March 2012. Subsequently, the Research and Development and the NHS management approval were granted.

The study population

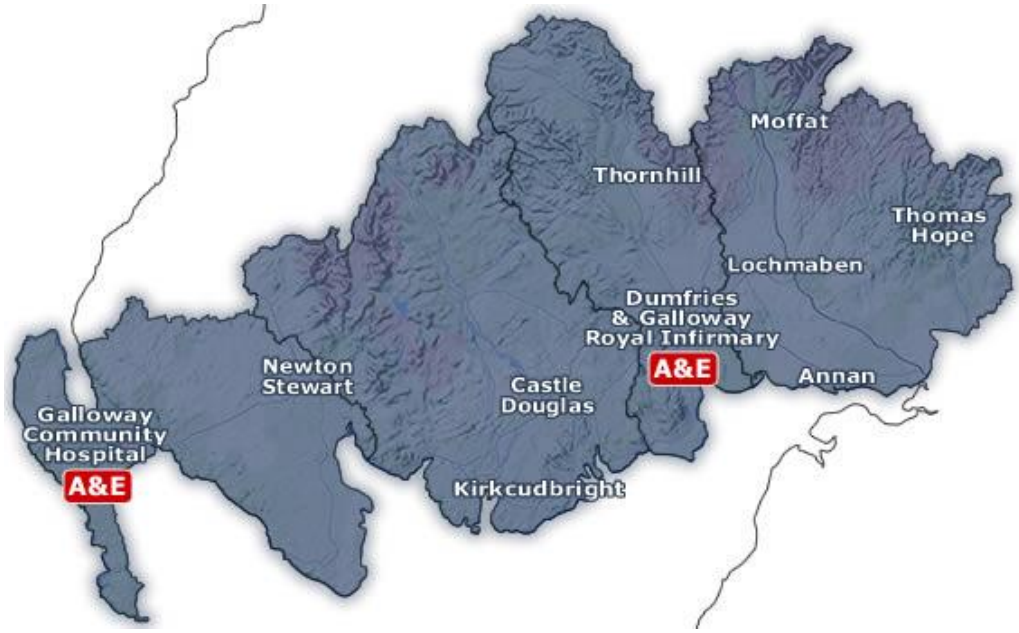
The population in Dumfries & Galloway is 148,190 (NHS Dumfries and Galloway 2 2013) which is scattered over a large geographical area of 2,400 square miles (Fig 3.2.2 and Fig 3.2.3), making it a rural population. About 36,500 women between the ages of 20-60 are eligible for cervical screening in this county. Of eligible women, 76.6% had been screened in the previous 3.5 years, and there were 6,109 cervical screening programme defaulters in January 2012.

There were 3498 defaulters between 30 and 55 years on 14th March 2012. A total of 1441 defaulters were found between the age of 20 years and 29 years on 3rd September 2012 and 648 defaulters between 56 and 60 years on 26th October 2012.

We targeted defaulters in the 30-60 year age group for HPV screening. Cytology screening only was offered to the younger 20-29 defaulters.

Fig 3.3.1: Geographical area of Dumfries and Galloway (Google Company USA 2014)

Fig 3.3.2: Distribution of NHS Dumfries & Galloway hospitals (NHS Dumfries and Galloway 2013)



Sample size considerations

The reported range of self-sampling uptake rate in eight population-based, large-scale self-testing studies was between 6.4% (Szarewski, Cadman et al. 2011) and 39.1% (Sanner, Wikstrom et al. 2009). The range of uptake rate of the standard smear (LBC) in those self-testing studies was between 4.1% (Szarewski, Cadman et al. 2011) and 17.6% (Bais, van Kemenade et al. 2007). We were hoping that 10-20% women would accept the HPV self-test and 5-10% women would accept the smear test because our target population tends to behave more like the population in London than in Sweden. We hypothesized that 15% of the target population of the 30-60 age group would accept self- sampling whilst it would be 7% for cervical smears.

Assuming 15% HPV self-sampling uptake rate, the width of the 95% confidence intervals based on 200, 1000 and 2000 invitations would be +/- 5%, +/- 2.5% and +/- 1.5% respectively.

STATA Version 12.0, SPSS Version 22.0 (Armonk, NY, USA) and Comprehensive Meta-Analysis Version 2.2.064 (Biostat Inc., NJ, USA) software was used for statistical analysis.

Timetable

Recruitment to all primary studies was carried out from 15th March 2012 to 31st December 2012. The follow up of vaginal HPV positive but, smear negatives (with a repeat smear test and colposcopy) was carried out from 17th June 2013 to 31st December 2013. Two women who were unable to attend in December re-scheduled for 19th January 2014.

Study design

The main study design was to offer vaginal self-sampling to defaulters aged between 30 and 60 years and to offer multiple options to have a smear test for defaulters aged between 20 and 29. Such defaulters were identified from the Scottish Cervical Call-Recall System by the Screening Services Manager, NHS Dumfries & Galloway. These defaulters were sent an initial letter (Fig 3.3.4, Fig 8.2.1, Fig 8.2.2), inviting them to consider various options (Fig 3.3.5, Fig 8.2.3) either to have a smear test or self-collect a vaginal sample for HPV screening.

Fig 3.3.4: The main body of the initial invitation letter (30-60 year old defaulters)

Your cervical screening test

We are writing to you because our records show that you are not up-to-date with your cervical smear test. Cervical screening tests enable us to detect the curable pre-cancerous stage of cervical cancer.

Around 1000 women die of cervical cancer in UK each year. However, most of those who develop it have not been screened regularly. Not going for cervical screening is one of the biggest risk factors for developing cervical cancer.

Attendance for a cervical screening test is therefore advised.

We recognise that some women (for a variety of reasons) do not attend the routine smear test appointment. We have therefore designed a study to offer women various options for getting a cervical screening test.

Fig 3.3.5: Option list (30-60 year old defaulters)

Options List (please tick the most suitable one for you)

1. I will make an appointment with my GP Practice or the Sexual Health Clinic to have a routine smear test. ☐
2. Please give me an appointment at a hospital clinic to have a routine smear test. ☐
3. Please give me an appointment at a hospital clinic. I prefer to collect a vaginal sample myself but under a supervision of a health professional. ☐
4. I would like to self collect a vaginal sample at home. ☐
5. I would like a doctor to contact me to discuss how I might get a test. ☐
6. None of above options suits me. ☐

Please tell us what arrangements might suit you or why you do not want a test

.....

Defaulters could also discuss anything with investigators or opt out. They were asked to inform us of their decision by retuning the options list which accompanied the initial letter. All options lists were returned to the Research and Development Department, where they were sorted and recorded appropriately by the Data Manager of the unit. The women's choice was facilitated appropriately (Fig 3.3.6). Women who wished to self-collect were sent a self-sampling kit with an information and consent pack with a pre-paid Royal Mail first class secure envelope. Vaginal samples were returned to Dumfries laboratory via the Research & Development Support Unit, where they were suspended in ThinPrep and were despatched to the Scottish HPV Reference Centre in Edinburgh for Hologic Cervista HPV-HR testing.

Each woman was informed of her HPV status in writing with adequate information. Whilst HPV positives were sent an appointment to have a smear test at the hospital smear clinic, which was dedicated for this purpose; HPV negatives were strongly advised to accept their next smear invitation. Women who were unable to come to the hospital were advised to have a smear test locally. In HPV positive women, smear (liquid based cytology, LBC) positives (borderline nuclear change or worse, >BNC) were referred to colposcopy as per local and Scottish guidelines. Smear negatives were advised to attend the annual follow-up clinic at the hospital. Women with any unsatisfactory test were offered a hospital smear clinic appointment to have a repeat cervical sample for LBC and HPV testing.

An annual follow-up appointment was sent about 12 months after the first smear test to HPV positive women who had at least had one smear test and who had not been referred to colposcopy. At the annual follow-up, the cervical smear was repeated and colposcopy was carried out according to the BSCCP guidelines and standards. Women diagnosed with CIN on punch biopsy were referred to another colposcopy clinic appropriately.

Fig 3.3.6: Study flow chart

Abbreviations: SCCRS = Scottish Cervical Call-Recall System; HPV =human papillomavirus; LBC=liquid based cytology; *Borderline dyskaryosis+

Contents of the self-sampling kit pack

1. The sealed, sterile Evalyn device which is placed inside a transparent, 'peel and seal' type plastic bag which measures (10x25cm). A white colour, absorbent pad (12x9cm) is also seen inside the plastic bag (packed according to the UN3373 standards packaging instruction P650).
2. A pre-paid, white colour jiffy bag (170x225cm) with the return address (Appendix 3.3)
3. Evalyn patient information leaflet (Appendix 3.1-3.2)
4. Questionnire-1 with a check list
5. Two copies of the consent form
6. The study's patient information leaflet
7. A list of frequently asked questions (Appendix 1)
8. A letter addressed to the participant

Methods of vaginal self-collection

The woman was advised to read the Evalyn brush patient information leaflet and our check list carefully, before the sample was collected. It is a two page leaflet with colorful illustrations (please see appendix 3).

The information leaflet instructs the female to spread the labia with one hand and insert the Evalyn brush into the vagina with the other, until the 'wings' of the Evalyn device come to contact with the labia. Then she is instructed to push the plunger (handle) in, hold it firmly and rotate the plunger 5 times clockwise, remove it and pull the plunger back, put the cap on and place it back in its plastic housing. This should be put in a transparent plastic bag which should be sealed after peeling its sticker off.

This plastic bag and the signed consent form and completed questionnaire were dispatched to Dumfries Laboratory in the pre-paid, first class mail jiffy bag provided. The woman was asked to put the large size envelope in a post box.

Methods of suspending vaginal Evalyn sample in ThinPrep vial

The Evalyn sample, the questionnaire and the consent form were all pre-labelled with the participant's name, a 10 digit CHI number, reference number and a barcode before the Evalyn kit was sent to the woman. The accuracy of all the patient identifiable data were cross-checked and recoded in the laboratory book before the sample was processed. The laboratory barcode label which comes in duplicate was placed on the ThinPrep vial and the laboratory book. The plastic bag was cut open with a pair of scissors. The seal of the ThinPrep vial was broken and the screw of the vial was loosened, but was not left open. A new pair of clean gloves was worn before each sample was processed. The cap of the Evalyn device was pulled out. The handle of the Evalyn was then pushed in so that the head of the Evalyn device would come out. With a new pair of clean, disposable, plastic tweezers, provided by Rovers Medical Devices, the plastic head of the Evalyn brush was pulled out and immediately put in the ThinPrep vial. The cap of the ThinPrep vial was then shut and vortexed for 2 minutes. The floating head of the Evalyn brush was then picked up to be discarded by a new pair of tweezers.

Methods of HPV DNA testing

1. The sample suspended in the PreservCyt solution is transferred from the ThinPrep pot to a 50mL Falcon tube.
2. They are then centrifuged at 1,110g for 10 min to pellet the cells.
3. All but 5mL of the PreservCyt is removed and the cells are re-suspended in the remaining 5mL of PreservCyt before being returned to the original ThinPrep pot.
4. ThinPrep pots are loaded onto the Hologic Sample Transfer System (STS 5000), in which 2mL of each sample are deposited into wells of a deep- well plate.
5. The deep-well plate (containing the 2mL aliquots of each sample) is loaded onto the Hologic HTA with the appropriate reagents to perform the Genfind script (this is the DNA extraction step).
6. The extracted DNA plate (containing the extracted DNA from each of the samples) is then reloaded onto the Hologic HTA (for research purposes only) with the appropriate reagents to perform the Cervista HPV HR script (this is the actual Cervista step).
7. Results are recorded/ reported appropriately.

The Cervista™ HPV HR test (Third Wave Technologies, Inc./Hologic Inc., Madison, WI,

USA) is a qualitative test for the detection of DNA from 14 high-risk HPV types, namely, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A positive result indicates that at least one of the 14 high-risk types is present in the DNA sample. The test uses the Invader® chemistry, a signal amplification method for detection of specific nucleic acid sequences. It has an internal control to detect genomic DNA so that the risk of a false negative result is low.

Methods of sample collection for LBC

Patients were asked to lie in the dorsal position and a plastic disposable Cusco's bivalve, self-retained vaginal speculum was introduced until the cervix was clearly visualized. Any profuse discharge or mucous was gently cleared with a large cotton bud. A cervical cytology sample was taken with a Rovers Cervex brush and an endocervical brush. The Cervex brush was put in the centre of the cervix ensuing that middle longer bristles were placed in the endocervical canal. It was rotated clockwise five times, maintaining adequate pressure, constantly. The endocervical brush sampler was then introduced inside the endocervix with the outermost bristles touching the ectocervix, rotated 1 time in a clockwise direction and then placed in the ThinPrep specimen collection tube as recommended by the manufacturer.

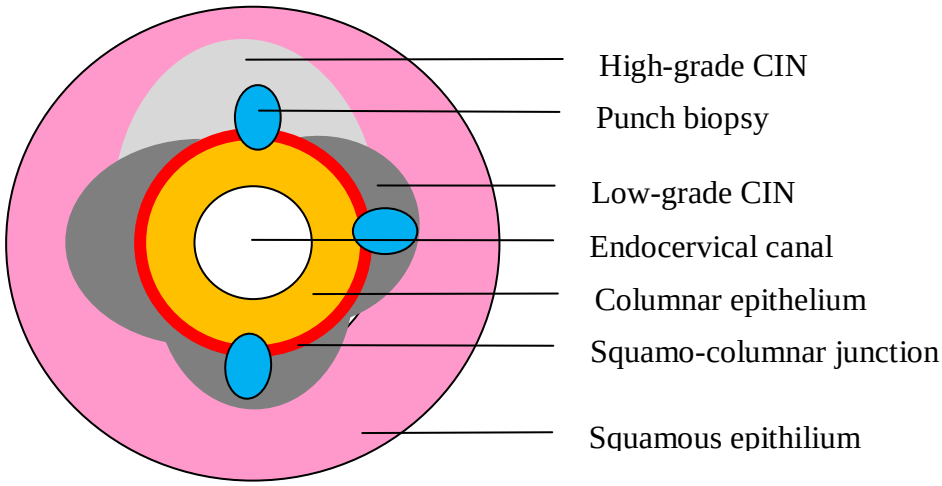
Methods of diagnostic colposcopy

Diagnostic colposcopy was carried out by British Society for Colposcopy and Cervical Pathology (BSCCP) accredited colposcopists at the Colposcopy Suite, Dumfries & Galloway Royal Infirmary. The NHS Cancer Screening Programme's colposcopy guidelines were followed. After application of 3% acetic acid, the entire transformation zone, the rest of the cervix and the vagina was systematically examined though the colposcope. Colposcopic features of any recognizable lesion were recorded on a colpograph. Visualizing the entire squamo-columnar junction and the upper end of the lesion, if any found, was always attempted. The Schiller's test was carried out using Schiller's iodine when indicated. Colposcopic directed punch biopsies were taken when the recognizably atypical transformation zone was present. Multiple biopsies were taken from lesions as necessary. No biopsy was taken if the colposcopy examination was normal. The colposcopic diagnosis of the lesion was recorded along with the colpograph

Methods of recording findings of diagnostic colposcopy

In order to explain colposcopic findings in a structured chart for recording colposcopy findings, I designed a colpograph (Fig 3.6.7) adhering to the BSCCP guidelines. This colpograph would give a reproducible, objective and schematic representation of the cervical disease. Aims of designing this colpograph were to precisely explain the extent to which HPV+ defaulters would have the HPV disease and to objectively appreciate the difference between the HPV screening and the cytology screening.

Fig 3.3.7: A detailed colpograph

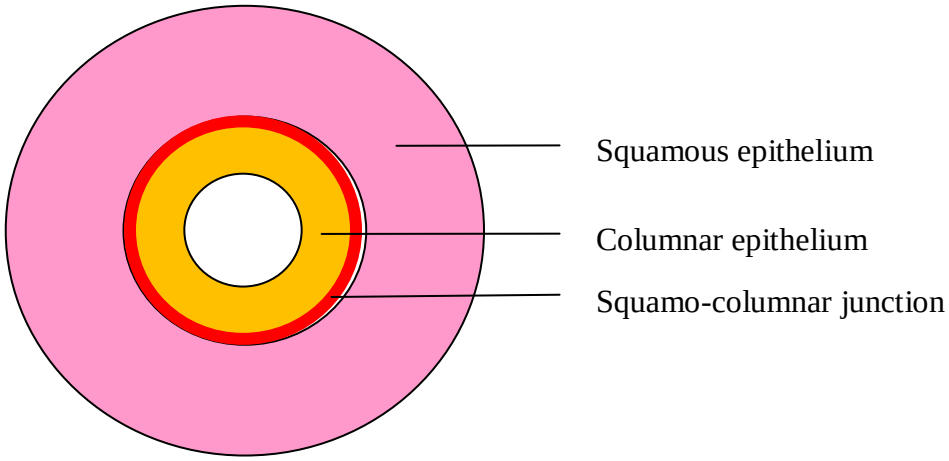


Types of transformation zones

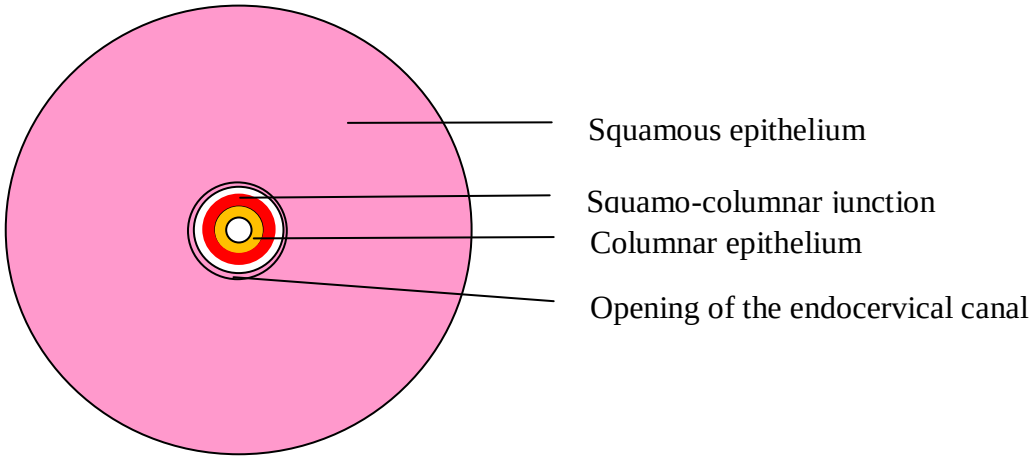
The anatomical junction where the endocervical columnar epithelium meets the ectocervical squamous epithelium is the squamo-columnar junction (SCJ). The anatomical location of the SCJ in relation to the external cervical os changes during the reproductive life mainly due to hormonal effects, giving rise to the original and new SCJ. The region (zone) between the original and the new SCJ is by definition is the transformation zone (TZ) (Fig 1.1.8). Whilst cells in the SCJ are most susceptible cells to HPV attack, TZ is the zone of the cervix where most HPV induced neoplasia (pre-cancer and cancer) develop. In other words, TZ (which includes SCJ) is the most vulnerable area of the cervix for HPV disease.

Fig 3.3.8: Different types of transformation zones

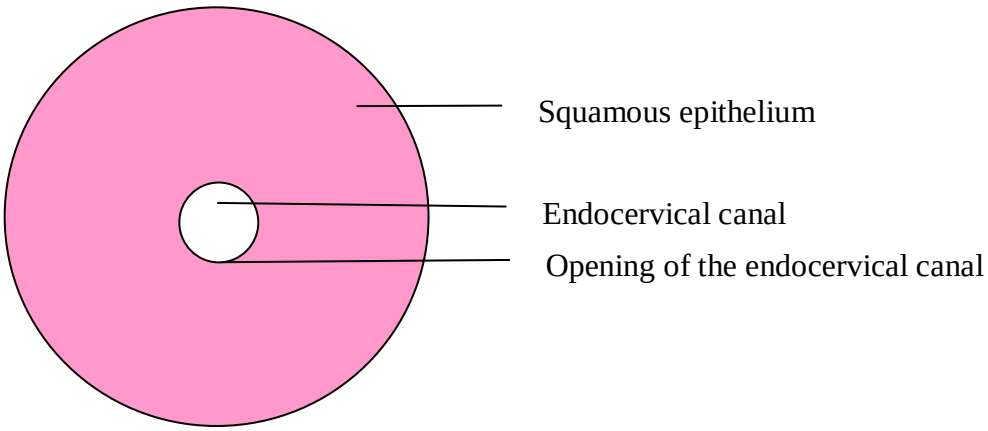
a) Type I TZ- SCJ is fully seen. It is completely ectovervical.



b) Type II TZ- the new SCJ is fully seen. The TZ has an endocervical component and may have an ectocervical component.



c) Type III TZ- SCJ is not seen. It recedes within the endocervical canal.



Definition of a Scottish Cervical Screening Programme defaulter

In simple terms, a screening eligible woman who is not up-to-date with her cervical smear test is a defaulter. This is, however, difficult to define.

In Scotland, cervical screening is offered to every woman with a cervix between the age of 20 years +1 day and 60 years and 364 days. The routine recall is every 3 years across the screening age group. There are 3 non-routine recalls based on the indication to repeat the test.

8. 3 months (inadequate smear)
9. 6 months (immediate post colposcopy or treatment)
10. 12 months (non-immediate follow-up after the treatment).

A woman becomes a defaulater if she has not been for testing 3 months after her final reminder. Defining a defaulter depends on the woman's recall advice. Women called routinely for screening are sent a prompt and two reminders whereas women requiring follow up are sent an additional reminder to attend for screening. A woman who has not attended a routine recall will be excluded from the recall and called a defaulter 9 months after being due for a smear (after a prompt and 2 reminder mailers at 0, 3 and 6 months, respectively Table 3.3.1). Therefore, a woman who has had a routine negative smear but no subsequent test will be called a defaulter 45 months (36+9) afte her normal test. Similarly, a 20 years and 9 months old woman who hasn't responded to recall letters will be a SCCRS defaulter (see example 1 in table 3.3.2).

Table 3.3.1: The Scottish cervical screening invitation intervals

	Prompt	**Reminder 1**	**Reminder 2**	**Reminder 3**	**Defaulter**
Routine Screening	When screening is due	3 months after prompt	3 months after 1st reminder	Not applicable	
Cumulative months	0	3	6	n/a	9-36
Non-routine Screening	When screening is due	2 months after prompt	2 months after 1st reminder	8 months after 2nd reminder	
Cumulative months	0	2	4	12	15-36

Defining a defaulter status for non-routine recall is more complex. A woman with a non-routine recall will be called a defaulter in 15 months of non-respondence (after receiving a prompt mailer at 0 months and 3 reminder letters at 2, 4 and 12 months: Table 3.3.1). A women who has had her first abnormal smear (e.g. mild dyskaryosis) today and has never attended a in a routine recall will be called a defaulter 21 months (6+15) later. If the recall has been 12 months (non-immediate follow-up after the treatment), the defaulter status starts at 27 months (12+15). If the recall has been 3 months (inadequate smear) the defaulter status starts at 18 months (3+15). A woman referred to colposcopy with an abnormal cytology who has failed to attend colposcopy clinic appointment/s will be sent reminders by the SCCRS similar to the standard non-routine defaulter. A prompt letter will be sent 5 months after the original colposcopy referral date and 3 reminders will be sent 2, 4 and 12 months after the prompt mailer.

Routine recall defaulters will be invited for a smear (will receive a prompt letter) 6 years (+0 months) from the date that woman last had a normal smear test by the SCCRS, A new invitation is sent after 4 years for non-routine recalls.

Examples of cervical screening recalls

If a woman in a routine recall (e.g. no previous abnormal smears) did not attend her smear which was due on month 36, she will be sent a prompt letter (initial invitation) on the 18th of the month that she was due for a smear. Assuming that she does not respond to any of these letters, she willl be sent the first reminder at 39 months and the second reminder at 42 months. She will be excluded from the recalling at 45 months and named a defaulter for the next 27 months (i.e. month 72). From the time of this invitation until after the reminders (72 to 81 months) she will not be considered a defaulter even though she does not go for screening (Fig 3.3.9a).

Fig 3.3.9a: Screening recall - routine

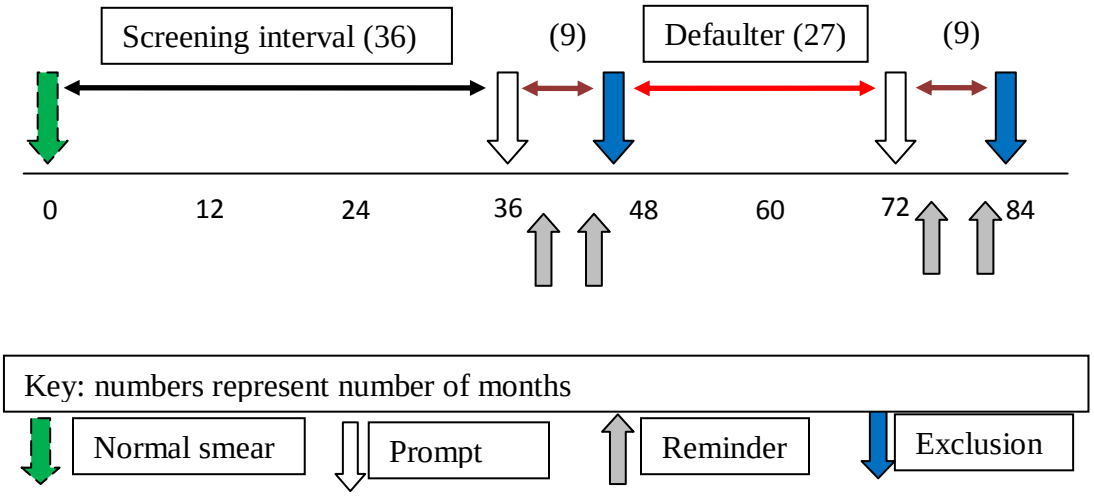
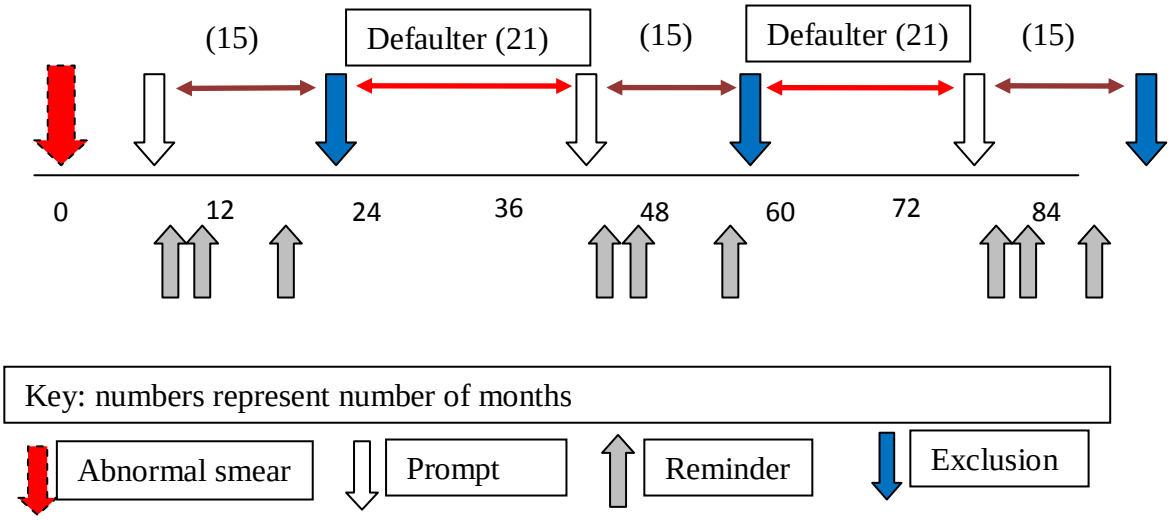


Fig 3.3.9b: Screening recall - non-routine



If a woman in a non-routine recall (e.g. a woman who has been up-to-date with her smears but the last smear test was reported as borderline dyskaryosis) has not attended her smear which was due in 6 months, she will be sent a prompt letter (initial invitation) in the month that she was due for a smear. Assuming that she does not respond to any of these letters, she willl be sent the first reminder at 8 months, the second reminder at 10 months and the third reminder at 18 months. She will be excluded from the recalling at 21 months and named a defaulter for the next 21 months. After 42 months since her last smear test, she will be sent the second batch of recalls (another prompt letter at 42 months followed by 3 reminders at 44, 46 and 54 months) (Fig 3.3.9b).

The interval between the abnormal smear test and the prompt letter depends on the type of abnormality and whether or not she has been treated. If it has been an inadequate test, the interval will be 3 months (example 3, table 3.3.2). For any other smear abnormality, including the ones who have failed to attend colposcopy, it is 6 months (example 5). For post treatment it can be either 6 months (immediate post treatment) or 12 months (long term follow-up until they get back to routine screning).

Table 3.3.2: Examples of different types of defaulters

	Description of the defaulter	Prompt letter	First reminder	Second reminder	Third reminder	Exclusion started	Projected recall
1	20 year old (DOB 03/10/91) who has never had a smear (RR)	18/10/2011 (0)	18/01/2012 (3)	18/04/2012 (6)	n/a	18/07/2012 (9)	18/10/2014 (36)
2	30 year old who has had a negative smear 12/11/08 (RR)	18/11/2011 (0)	18/02/2012 (3)	18/05/2012 (6)	n/a	18/08/2012 (9)	18/11/2014 (36)
3	30 year old who has had a unsatisfactory smear 31/01/08 (NR)	18/05/2011 (0)	18/07/2011 (2)	18/09/2011 (4)	18/05/2012 (12)	18/08/2012 (15)	18/05/2014 (36)
4	28 year old who had CIN2 21/11/06 & negative smear 12/05/10 (NR)	18/05/2011 (0)	18/07/2011 (2)	18/09/2011 (4)	18/05/2012 (12)	18/08/2012 (15)	18/05/2014 (36)
5	32 year old who had moderate dysk on her 3rd smear 07/07/09 (NR)	18/12/2009 (0)	18/02/2010 (2)	18/04/2010 (4)	18/12/2010 (12)	Had a smear 01/03/2011 severe	Attended colposco 14/04/2011

Only the last cycle of recall is illustrated. The number of months since the screening has been due is in brackets. RR= routine recall. NR= non-routine recall.

CHAPTER 4

Interventional studies to offer screening to defaulters

4.1: The 1000 defaulter study

Study question

Can cervical screening participation be improved by sending multiple screening options letters to defaulters aged 30-55 years?

Summary answer

The total positive response rate was 24% (21%-26%) (236/1000). Whilst 129 (13%) defaulters opted-in for self-sampling, 92 (9%) samples were received.

What is known and what this study adds

Sending a self-sampling kit to defaulters is known to increase the screening participation. This study showed that sending a letter offering multiple screening options which includes self-sampling increases cervical screening uptake rate.

Limitations

It was not possible to check the screening status of defaulters 6 months after the intervention so the total number of defaulters screened is unknown.

Methods

The aim of the three studies in defaulters aged 30-55 was to investigate whether it was possible to increase cervical screening participation in screening defaulters by increasing their options for screening. In particular to see whether defaulter aged 30-55 years would choose to provide a self-sample for HPV testing. Rather than inviting all defaulters in one go, it was decided to invite them in stages so as to ensure that we would be able to deal with all requests for screening promptly and so that if necessary the protocol could be modified in response to lessons learnt from the first wave of invitations. The first study aimed to offer 1000 defaulters several options for cervical screening.

The addresses and vital status of all women in the 30-55 year old defaulter database were cross-checked against the hospital database (TOPAS Patient Administrative System) by the data manager of the Research & Development Support Unit. The database was ordered by the community health index (CHI) number. We continued cleaning the database until we had 1000 valid live subjects with addresses that were the same in the two databases. We examined 1246

women in order to identify 1000 to invite. Five women were found to be deceased; two had left the country; and 239 were excluded either because the addresses in the two databases did not match or because no address was found in the TOPAS database.

All of these 1000 women were sent the initial invitation letter (Fig 3.3.4) inviting them to select one option from a list of six (Fig 3.3.5). Invitations were posted by second class mail between 15 March 2012 and 20 April 2012. Those who did not respond within 3 months were sent a reminder letter with the same options.

Women requesting to do HPV testing at home were sent a self-sampling kit. Women who have asked for an appointment at a hospital clinic for a HPV test (option-3) were counselled at the clinic. They were offered two options: to self-collect a vaginal sample with the Evalyn brush under direct supervision of the clinician or to allow clinician to collect a vaginal sample with the Evalyn brush adhering to manufacturer's self-sampling steps [please see details in chapter 3]. All women requesting a hospital HPV test asked the clinician to collect the sample. Women requesting a cervical smear test at a hospital clinic were offered an appointment and those who attended had a speculum examination and a cervical sample taken by a clinician.

Women testing HPV positive on their self-sample were encouraged to have a smear taken at the hospital clinic. All women who came to the hospital smear clinic were offered dual testing: LBC with HPV testing of the residual. The clinician-collected cervical samples were first used to prepare a LBC slide, and residual material was used for HPV testing (reflex HPV testing). All HPV tests used the Cervista assay [please see details of laboratory methods in chapter 3]

Women who returned the option questionnaire consented to being following in the SCCRS database and details of any subsequent cervical screening in these women were noted. We did not have permission to access the screening records of women who did not return their options list.

The age of the woman, the time since her last smear test and the type of defaulter (previously routine, previously early recall following borderline changes, etc.) were recorded.

Results

A total of 258 option lists were returned (Table 4.1.1). The first option (to have a routine screening at the GP practice) was ticked by 63 (6%), the second (to be screened at a hospital clinic) was ticked by 23 (2%), the third (HPV testing at a hospital clinic) was ticked by 5 (1%), the fourth (HPV testing of a self-sample) by 129 (13%), the fifth (discuss) by 16 (2%) and the sixth (opt out) by 22 (2%). According to the number of option lists returned, the total positive response rate (excluding those who opted out) was 209 (21%). I was unable to determine the number of women who had smears at their GP practice without returning the option list.

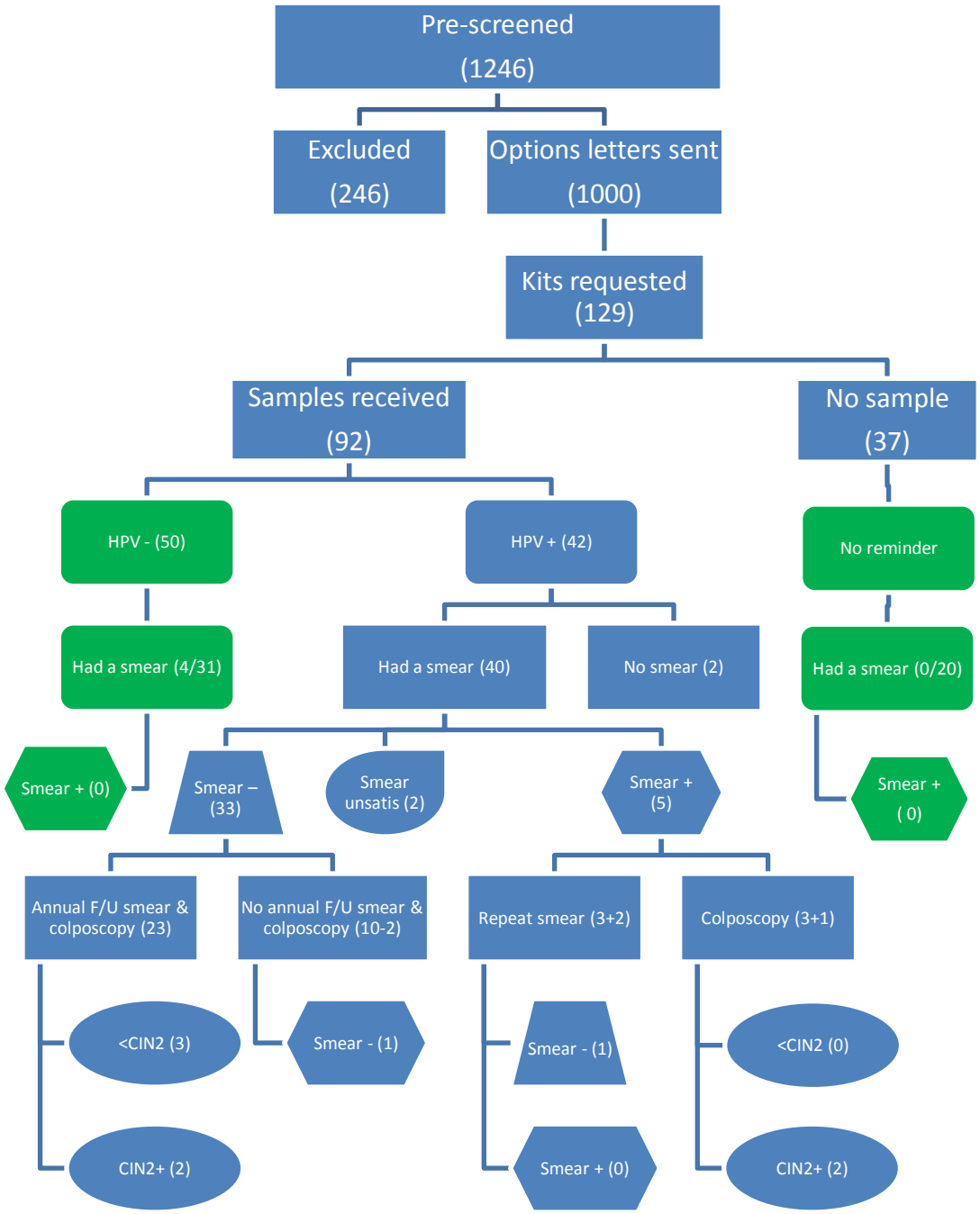
Table 4.1.1: Response in the 1000 defaulter study at 6 months

Option	Description	n	**%**
1	Smear at GP	63	**6**
2	Smear at hospital clinic	23	**2**
3	HPV testing at hospital clinic	5	**1**
4	HPV testing at home	129	**13**
5	Wanted to discuss	16	**2**
6	Opt out	22	**2**
	Total positive response	236	**24**

About a third (40/129=31%) of those requesting a self-sampling kit (option 4) did so only after receiving the reminder letter. In other words, 89/1000 requested a kit within the first 3 months. Only two requests for the option-2 were received after the reminder and there were no option-3 or option-5. About a dozen of option-1 and a similar number of option-6 were returned after receiving the reminder.

Women in the 1000 defaulter study who opted to self-collect (n=129) had median age of 44 years with inter quartile range 39-52 years. The mean duration for which these defaulters had not been screened (duration since the last smear test, if any, or from 20 years of age otherwise) was 9.0 years, standard deviation 5.6 years. The median was 8 years with IQR of 5-11 years. Fourteen (11%) had never been screened. There were 5 women on the non-routine recall category with a previous non-normal smear. Times since last smear test of these 5 women were 2 years (unsatisfactory), 3 years (borderline dyskaryosis), 3 years (borderline dyskaryosis), 3 years (unsatisfactory) and 7 years (borderline dyskaryosis).

Fig 4.1.1: HPV screening and follow-up summary of the 1000 defaulter study



Abbreviations: HPV+= HPV positive; HPV-= HPV negative; smear+= smear positive; smear-= smear negative; <CIN2= low-grade CIN or less; CIN2+= high-grade CIN or worse; F/U= follow-up. The number of women is indicated within brackets.

Of the 129 women who requested a self-sampling kit, 92 (71%) returned a sample (Fig 4.1.1). Fifty (54%) of them were HPV negative, 42 (46%) were HPV positive. Almost all (40/42= 95%) HPV positives subsequently had a smear test. One woman who did not come for a smear test informed us that she would have it at her new GP practice in England as she was planning move away from Scotland at the end of 2012.

A total of 40 smears were carried out in women who were HPV positive on their self-sample. Whilst the majority (n=38) came to the hospital smear clinic, two HPV positive women had smears at their own GP Practice. All were within 12 months of self-sampling.

Thirty-three (83%) smear tests were reported as negative. There were 2 severe dyskaryosis, 2 mild (low-grade) dyskaryosis, 1 borderline changes and 2 unsatisfactory smears. Two women with severe dyskarysis, one HIV positive woman with borderline dyskaryosis and one woman with persistent unsatisfactory smears were referred to colposcopy. Whilst the former 2 patients had CIN3, the latter woman had genital atrophy (no CIN detected). The HIV positive woman failed to attend her colposcopy appointment twice. Follow-up smears were arranged for all women. The HIV positive woman had borderline changes 4 months after the first smear test. As of 10 June 2014 she hadn't had any further smears. Both women with 2 unsatisfactory smears have had 2 satisfactory and negative smears, subsequently. One sample was not retained (after LBC) for HPV testing by error. Of 35 smear residuals with a valid HPV result, 14 (40%) had a positive HPV result (Table 8.1.1, Appendix 1). Residual samples of 2 smears which were taken in the community were not tested for HPV.

Women with high grade CIN were referred to the Clinical Supervisor's colposcopy clinic immediately. Women with low-grade CIN were referred to the same clinician to be seen at the colposcopy clinic in 6 months, keeping with local management guidelines. Women with hgCIN have had LETTZ treatment.

Women who have had a negative smear following a positive vaginal HPV result in 2012 were invited to attend the annual follow-up clinic in 2013, approximately 12 months after the first smear test. Women who were referred to colposcopy in 2012 (n=4) and HPV positive women who did not attend the smear test in the first round in 2012 (n=2) were not invited to the annual follow-up. A total of 33 HPV positive were invited to the annual follow-up clinic. The majority, 23/33=70% have attended the annual follow-up clinic. One of them decided to have a smear

test at the GP. At the annual follow-up clinic, the woman's informed written consent was obtained for a repeat cervical smear test, diagnostic colposcopy ±punch biopsy. Colposcopic diagnosis was low grade CIN in 3 women, high grade CIN in 2 and suspected low grade CIN in one case. Punch biopsy confirmed above diagnosis except in the woman with suspected lgCIN, who was found to have cervicitis.

Of the 50 women who tested negative for HPV, 31 were invited for a smear test by SCCRS by 31 December 2013 (Fig 4.1.1). Four women (13%) have had a smear test. Although 20 women in the group that did not return a sample were called by SCCRS for a smear, none of them have had a smear test during the same period of time. This is simply an observation made by checking individual's screening status in the SCCRS which is passive follow-up rather than any intervention.

4.2: The 200 defaulter study

Study question

Can cervical screening participation be improved by sending a self-sampling kit with multiple screening options letter to defaulters aged 30-55 years?

Summary answer

The total positive response rate was 32% (25%-38%) [63/200]. A total of 40 (20%) self-collected samples were returned.

What is known and what this study adds

Sending a self-sampling kit to defaulters is known to significantly increase the screening participation. Evalyn self-sampling device was not previously used for community based self-sampling studies. Evalyn brush was well accepted by defaulters in this study.

Limitations

Sample size was limited to 200.

Methods

This second study aimed to offer 200 defaulters several options for cervical screening, which included sending a self-sampling kit with the initial invitation letter.

The addresses and vital status of women in the 30-55 year old defaulter database were cross-checked against the hospital database (TOPAS Patient Administrative System) by the data manager of the Research & Development Support Unit. The database was ordered by the community health index (CHI) number [please see details in chapter 1.3]. We continued cleaning the database until we had 200 valid live subjects with addresses that were the same in the two databases. We examined 221 women in order to identify 200 to invite. One woman was found to be deceased and 20 were excluded either because the addresses in the two databases did not match or because no address was found in the TOPAS database.

All of these 200 women were sent a self-sampling kit with the initial invitation letter (Fig 3.3.4) inviting them to select one option from a list of six (Fig 3.3.4). Invitations were posted by second

class mail between 18 June 2012 and 22 June 2012. Those who did not respond within 3 months were sent only a reminder letter with the same list of options (without a kit).

Management of women was identical to that used in the 1000 women study. Women requesting a cervical smear test at a hospital clinic were offered an appointment and those who attended had a speculum examination and a cervical sample taken by a clinician. Women testing HPV positive on their self-sample were encouraged to have a smear taken at the hospital clinic. All women who came to the hospital smear clinic were offered dual testing: LBC with HPV testing of the residual.

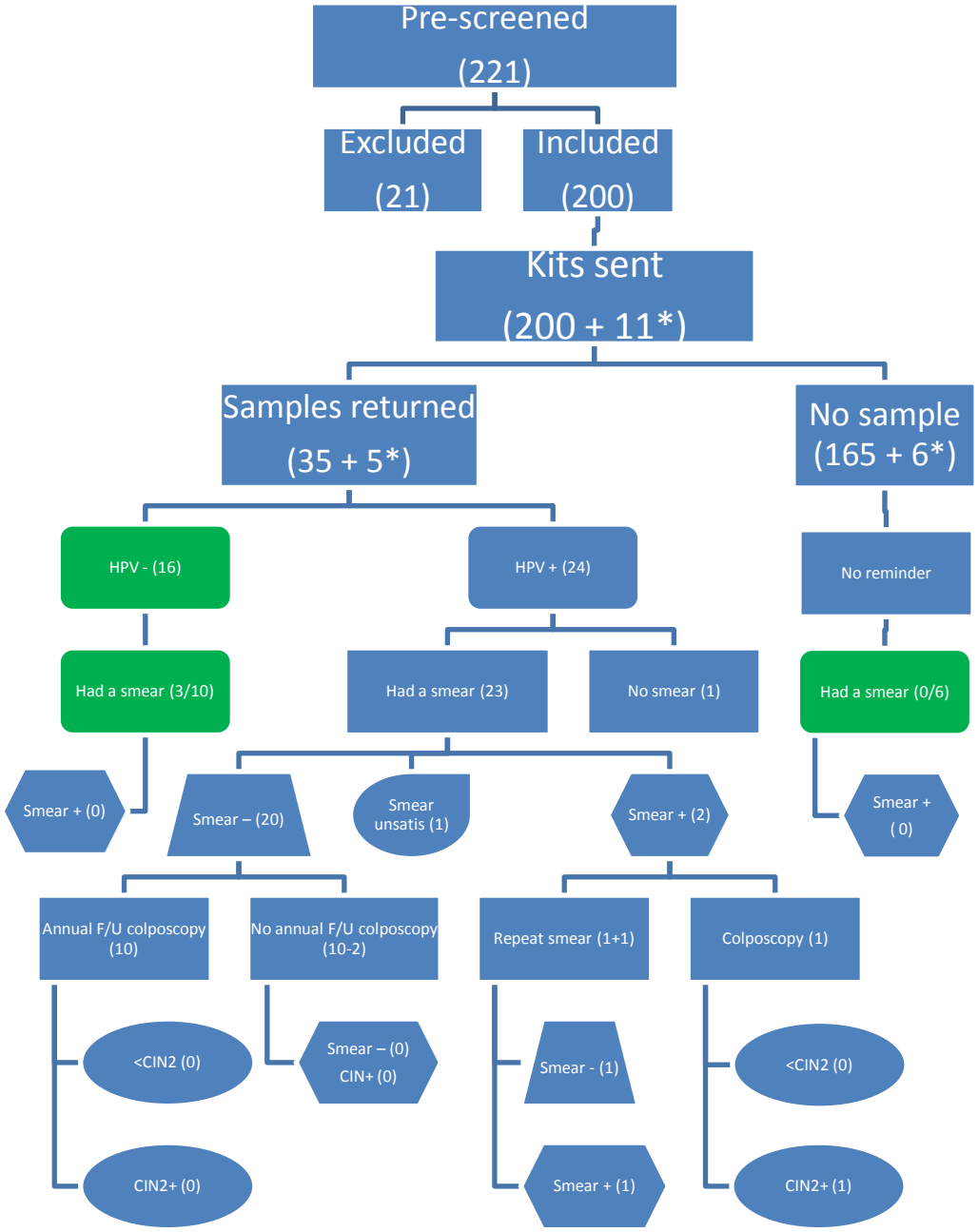
Results

A total of 72 (36%) option lists were returned. The first option (to have a routine screening at the GP practice) was ticked by 8 (4%), the second (to be screened at a hospital clinic) was ticked by 5 (3%), the third (HPV testing at a hospital clinic) was ticked by 0, the fifth (discuss) by 4 (2%) and the sixth (opt out) by 3 (2%). A total of 35 samples (option four) were received within 3 months of being sent out (the first round). The fourth option (HPV testing of a self-sample) was ticked by a further 11 (6%) after receiving the reminder at 3 months (in the second round). Consequently, 11 Evalyn kits were sent in the second round, but only 5 were returned with a sample (Fig 4.2.1). According to the number of self –samples received or the number of option lists returned, the total positive response rate (excluding those who opted out) was 63 (32%, including 4 'discuss' and 6 who requested a kit but did not return a sample). I was unable to determine the number of women who had smears at their GP practice without returning the option list. Therefore, the total screening uptake rate of this cohort is unknown.

Table 4.2.1: Response in the 200 defaulter study at 6 months

Option		n	**%**
1	Smear at GP	8	**4**
2	Smear at hospital clinic	5	**3**
3	HPV testing at hospital clinic	0	**0**
4	HPV testing at home	46	**23**
5	Wanted to discuss	4	**2**
6	Opt out	3	**2**
	Total positive response	63	**32**

Fig 4.2.1: HPV screening and follow-up summary of the 200 defaulter study



Abbreviations: *Women who ticked option-4 only after receiving the reminder letter were sent a second kit; HPV+= HPV positive; HPV-= HPV negative; smear+= smear positive; smear-= smear negative; <CIN2= low-grade CIN or less; CIN2+= high-grade CIN or worse; F/U= follow-up. The number of women is indicated within brackets.

A majority of samples returned (35/40=88%) were from the first round, i.e. within the first 3 months. Twenty (10%) samples were received within a week. Another 11 samples were received in next 3 weeks. Only two requests for the option-1 were received after the reminder and there were no option-2, option-3 option-5 or option-6. The research team received 7 telephone calls after defaulters received the kit with the initial invitation letter. Whilst screening was not indicated for 3 of them, 4 women wished to get a smear test. The research team received 6 telephone calls after defaulters receiving the reminder letter. Whilst screening was not indicated for 4 of them, 2 women wished to get a smear test.

Women in the 200 defaulter study who either self-collected (n=35) or wished to do so (n=11) were all aged 32-55: the median age was 45 years with inter quartile range 39-52 years. The mean duration for which these defaulters had not been screened (duration since the last smear test, if any, or from 20 years of age otherwise) was 7.8 years, standard deviation 3.9 years. The median was 6.0 years with IQR of 5-9 years. Four (9%) had never been screened. There were 5 women on the non-routine recall category with a previous non-normal smear. Times since last smear test of these 5 women were 3 years (unsatisfactory), 4 years (borderline dyskaryosis), 4 years (borderline dyskaryosis), 8 years (borderline dyskaryosis) and 11 years (unsatisfactory). That is, none of them had been screened within the last three years.

Thirty five out of 200 kits which were sent in the 3rd week of June were returned with a sample. Of the 11 women who requested a self-sampling kit, 5 (45%) women returned a sample (Fig 4.2.1). Sixteen (40%) of the 40 were HPV negative, 24 (60%) were HPV positive. All except one 23/24 (96%) HPV positives subsequently had a smear test. Whilst the majority (n=18) came to the hospital smear clinic, 5 HPV positive women had smears at their own GP Practice. All were within 12 months of self-sampling.

Twenty of 23 (87%) smear tests were reported as negative. There was 1 severe dyskaryosis, 1 borderline dyskaryosis and 1 unsatisfactory smears. The woman with severe dyskaryosis was referred to colposcopy. She was diagnosed with CIN2 on LEETZ biopsy. Of 16 smear residuals with a valid HPV result, 6 (38%) had a positive HPV result (Table 8.1.2, Appendix 1).

Women who have had a negative smear following a positive vaginal HPV result in 2012 were invited to attend the annual follow-up clinic in 2013, approximately 12 months after the first smear test. The woman who was referred to colposcopy in 2012, the woman who has had a

total abdominal hysterectomy and the HPV positive woman who did not attend the smear test in the first round in 2012 were not invited to the annual follow-up. A total of 21 HPV positive were invited to the annual follow-up clinic. About half, 11/52=52% have attended the annual follow-up clinic. Two of them decided to have a smear test at the GP. At the annual follow-up clinic, woman's informed written consent was obtained for a repeat cervical smear test, diagnostic colposcopy ±punch biopsy.

A total of 11 women had both cervical smear and diagnostic colposcopy. The colposcopic diagnosis was high grade CIN in 1 case and low grade CIN in 1 case and normal in the other 9 cases. Whilst a LLETZ biopsy was taken from the woman with the high-grade CIN, multiple punch biopsies were taken from the woman with low-grade CIN. Histology confirmed the hgCIN. Suspected lgCIN was diagnosed to have cervicitis.

Of the 16 women who tested negative for HPV on self-sample, 10 were invited for a smear test by SCCRS by 31 December 2013 (Fig 4.1.1). Three women (30%) have had a smear test. Although 6/11 women in the group that did not return a sample were called by SCCRS for a smear, none of them have had a smear test during the same period of time. This is simply an observation made by checking individual's screening status in the SCCRS which is passive follow-up rather than any intervention.

4.3: The 2000 defaulter study

Study question

Can the screening participation be improved by sending multiple screening options letter to defaulters aged 30-55 years?

Summary answer

The total positive response rate was 16% (14%-18%) [325/2031]. Whilst 158 (8%) opted for self-sampling; only 108 (5.3%) samples were received.

What is known and what this study adds

Sending a self-sampling kit to defaulters is known to significantly increase the screening participation. If the self-sampling kit could be supplied on-demand, it could be cost-effective. Defaulters' response was relatively low in this study in comparison to 1000 defaulter study where 'list cleaning' was carried out, which may adversely affect the cost-effectiveness of this method.

Limitations

No 'list cleaning' may have contributed to the lower response rate.

Methods

This third study aimed to offer 2000+ defaulters several options for cervical screening, which included the option of ordering a self-sampling kit for HPV screening. We allocated all remaining (2031) defaulters in the 30-55 year old database of 3498 without list cleaning.

Addresses of these women had NOT been cross-checked against the hospital database (TOPAS). Women who did not respond were sent a reminder and the Questionnaire in 2 months. Methodology of this study was otherwise similar to that of the study 4.1.

First batch of invitation letters were sent 7-20 July 2012. Reminder letters were sent 5-9 September.

Results

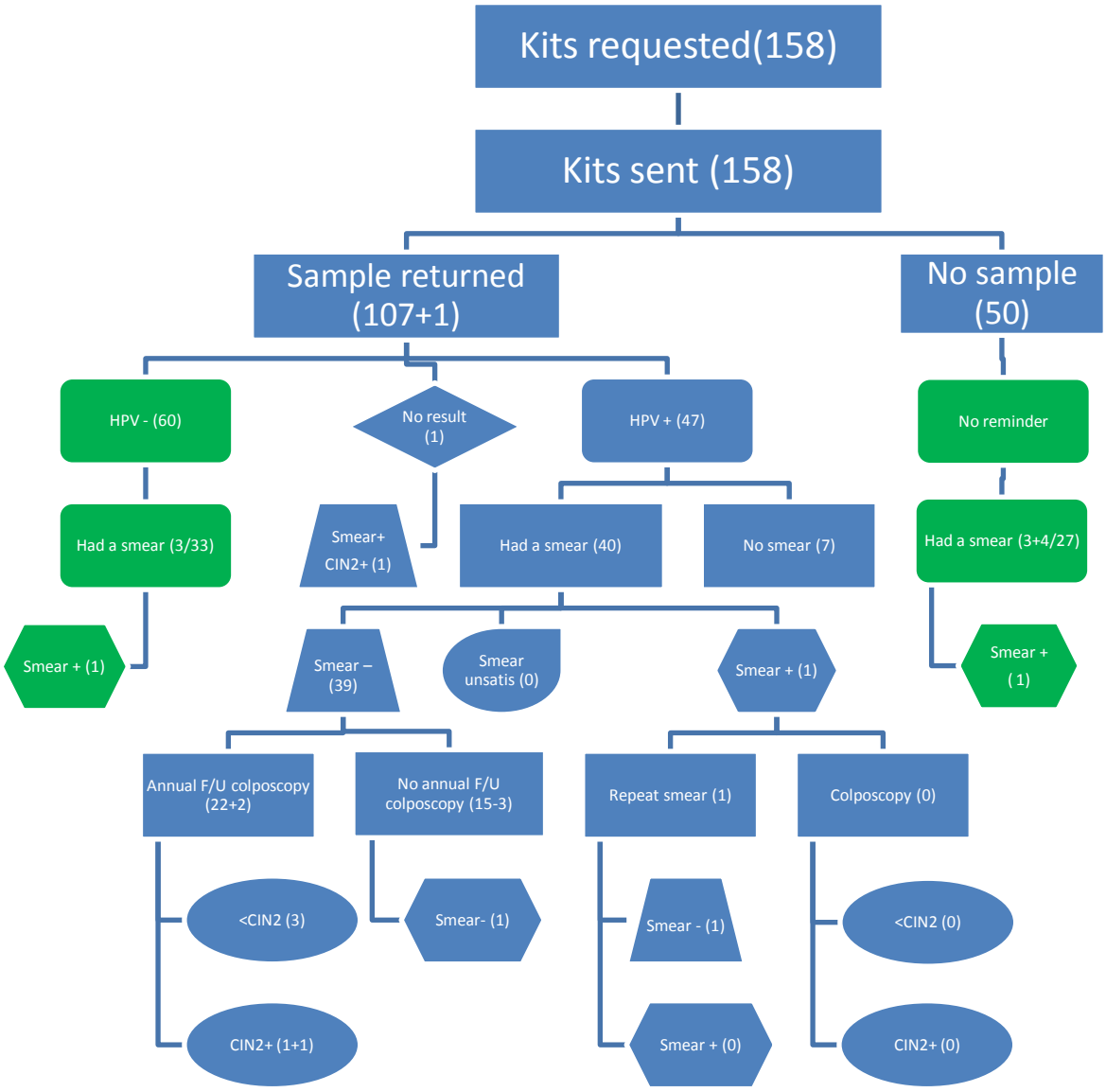
A total of 371 (18%) option lists were returned. The first option (to have a routine screening at the GP practice) was ticked by 108 (5%), the second (to be screened at a hospital clinic) was ticked by 40 (2%), the third (HPV testing at a hospital clinic) was ticked by 3 (0%), the fourth (self-sampling at home) by 158 (8%), the fifth (discuss) by 16 (1%) and the sixth (opt out) by 46 (2%). A total of 107 samples (option four) were received within 3 months of being sent out (the first round). I was unable to determine the number of women who had smears at their GP practice without returning the option list.

Table 4.3.1: Response in the 2000 defaulter study at 6 months

Option		n	**%**
1	Smear at GP	108	**5**
2	Smear at hospital clinic	40	**2**
3	HPV testing at hospital clinic	3	**0**
4	HPV testing at home	158	**8**
5	Wanted to discuss	16	**1**
6	Opt out	46	**2**
	Total positive response	325	**16**

A small proportion (22/158=14%) of those requesting a self-sampling kit (option 4) did so only after receiving the reminder letter. Twenty six women chose the option-1 in response to the reminder letter. Only two requests for the option-2 were received after the reminder and there were no option-3. Three women selected the option-5, 18 women selected the option-6 in response to the reminder. The research team received 19 telephone calls in the first round. Screening was not indicated for 14 of them, 5 women wished to get a smear test at the community. The research team received 10 telephone calls in the second round. Whilst screening was not indicated for 6 of them, 4 women wished to get a smear test at the community. Two emails from the 2000 study group were received during the first round, clarifying if they should be screened. Screening was not indicated for either of them.

Fig 4.3.1: HPV screening and follow-up summary of the 2000 defaulter study



Abbreviations: HPV+= HPV positive; HPV-= HPV negative; smear+= smear positive; smear-= smear negative; <CIN2= low-grade CIN or less; CIN2+= high-grade CIN or worse; F/U= follow-up. The number of women is indicated within brackets.

Women in the 2000 defaulter study who wished to self-collect (n=158) were aged 30-55: the median age was 43.0 years with inter quartile range 37-50 years. The mean duration for which these defaulters had not been screened (duration since the last smear test, if any, or from 20 years of age otherwise) was 8.1 years, standard deviation 5.0 years. The median was 7.0 years with IQR of 5-10 years. Fourteen (11%) of these women had never been screened. There were 5 women on the non-routine recall category with a previous non-normal smear, who should have been screened 3-12 months after the previous smear test. The duration since the last smear test of these 5 women was 2 years (unsatisfactory), 3 years (BNC), 3 years (BNC), 3 years (unsatisfactory) and 7 years (BNC) years.

One hundred and eight out of 158 kits which were sent were returned with a sample. One sample was returned a long time after the study had stopped. She has subsequently had a smear test. Out of 107 self-collected samples, 60 of them were HPV negative, 47 were HPV positive. A vast majority 41/47 (87%) HPV positives came for a smear test. Whilst the majority (n=34) came to the hospital smear clinic, 7 HPV positive women had smears at their own GP Practice. All were within 12 months of self-sampling. It was not possible to do a cervical smear in one woman because her cervix was covered with enlarged fibroids.

All except one (39/40) smear tests were negative. A 51 year old woman had a borderline dyskaryosis in September 2012, but she has had 2 negative (normal) smears in June and December 2013.

Residuals of 7 smears which were taken in the community were not tested for HPV. Four smear residuals were not retained for HPV testing by error. Of 26 smear residuals with a valid HPV result, 3 (12%) had a positive HPV result (Table 8.1.3, Appendix 1).

Women who have had a negative smear following a positive vaginal HPV result in 2012 were invited to attend the annual follow-up clinic in 2013, approximately 12 months after the first smear test. A total of 33 HPV positive were invited to the annual follow-up clinic. A majority, 24/33=73% have attended the annual follow-up clinic. Two of them decided to have a smear test at the GP, after receiving the annual follow-up colposcopy invitation. At the annual follow-up clinic, the woman's informed written consent was obtained for a repeat cervical smear test, diagnostic colposcopy ±punch biopsy.

A total of 24 women had both cervical smear and diagnostic colposcopy. The colposcopic diagnosis was high grade CIN in 4 cases, low grade CIN in 4 cases, suspected low-grade in 3 cases and normal in the 11 cases. Two colposcopies were deemed unsatisfactory (inadequate) as the entire transformation zone was not visualised, but colposcopy examinations were normal otherwise. Whilst a LLETZ biopsies were taken from the woman who has had colposcopy under general anaesthesia (please see below) and the woman with moderate dyskaryosis, women with the high-grade CIN, multiple punch biopsies were taken from the woman with low-grade CIN. Histology confirmed hgCIN in 3 out of 4 colposcopic diagnoses. Histological diagnosis was available for 3 out of 4 lgCIN. Histology confirmed the diagnosis in 2 out of 3 cases. Histological diagnosis was available for 2 out of 3 suspected cases of lgCIN. None of them had any CIN.

Of the 60 women who were tested negative for HPV, 33 were invited for a smear test by 31 December 2013. Three women (9%) have had a smear test. Three women in the group that did not return a vaginal sample have been to a smear test during the study period in 2012. Of the remaining 48 women, 27 have been called by SCCRS for smears in 2013, 4 of them have had smear tests by 31 December 2013. One of them was a borderline nuclear change, she is due for a repeat smear in 6 months.

There were 4 interesting cases in this cohort which are worth reporting in detail.

A 41 year old individual who underwent gender re-assignment was one of our study participants. This person disclosed that he is genetically a female who underwent subtotal hysterectomy 1 year ago. Although a total hysterectomy was planned, gynaecologists had to leave the cervix as it was technically very difficult to remove it. This person would not allow GP or Practice Nurse to take a smear. He stated that self-sampling would be the only way that a transgender person can get screened. Self-collected sample was HPV positive. He refused to come to the smear clinic as he did not want to attend a female clinic. He would not even come to the female ward to have a smear test. He will never get this done at the GP practice. In the meantime, he was referred to Gynaecology by his GP as he was requesting the remaining cervical stump to be removed for various reasons. This has since been carried out in the theatre under general anaesthesia. A cervical smear was taken prior to diagnostic colposcopy which was subsequently reported as negative. Colposcopy diagnosed a type 2 transformation zone and high grade CIN. LETTZ confirmed CIN2.

A 53 year old defaulter asked for a self-sampling kit and also for us to contact her. This person had multiple unsuccessful attempts of getting a smear test. The last 2 smear tests had been reported unsatisfactory in 2009. She explained that there are vaginal 'tumours' obstructing the cervix, which make taking a smear impossible. This anxious patient who was worried about this was seen at the colposcopy clinic by the clinical supervisor, but smear could not be taken as the cervix was not seen. It was completely obliterated with a growth which was assumed to be a fibroid. A MRI scan had been arranged. The MRI scan in April 2013 has been reported as follows: "there is a large mass measuring 5.5 x 4.3 x 4 .5 cm, occupying most of the upper vagina and continuous with the cervix. There is no evidence of soft tissue extension into the parametrial tissues. There is no significant pelvic or inguinal lymphadenopathy. On histological confirmation, the suggested stage is TIIa". However, staging is not relevant without histological confirmation. Multiple attempts to offer her treatment have been unsuccessful.

A 43 year old defaulter requested a self-sampling kit after receiving the reminder letter. Her last smear test was 13 years ago which was normal. She had a borderline smear in 1992. She had 2 normal smears afterwards. She contacted us in March 2013 asking HPV test results, after we have stopped testing samples for HPV. She said that although she has sent a sample for HPV testing before, she hasn't received the result of it. This sounded very unusual, because no previous sample had been lost. We checked our database which confirmed that she was sent a kit on 5 October 2012, but no sample received. Participant was adamant that she posted the sample that she self-collected. We immediately offered her an appointment for a smear test, for which she attended. Smear was reported to be moderate dyskaryosis. Colposcopy revealed a HGCIN. LETTZ histology confirmed CIN3.

A 34 year old defaulter who had 2 borderline smears in 2001 and another 2 borderline smears in 2006 had a normal smear in March 2007. She had not been to a smear since then. Vaginal HPV screening was negative. She had been to a smear test in August 2013, soon after receiving the second reminder letter. This smear was reported as BNC was referred to colposcopy by SCCRS. Colposcopy in early October revealed possible lgCIN. Two punch biopsies taken 2x3mm each. Histopathological diagnosis was squamous metaplasia.

4.4 The older defaulters study.

Study question

Can the screening participation be improved by offering multiple screening options to defaulters aged 56-60 years?

Summary answer

The total screening uptake rate in the 'letter' group (14%) was not significantly increased in comparison to the control group (6%). The total screening uptake rate in the 'kit' group (17%) was significantly increased (RR=2.7, 1.0-7.2) in comparison to the control group. The difference between the kit group and the letter group was not significant.

What is known and what this study adds

Sending a self-sampling kit to defaulters is known to significantly increase the screening participation. The total screening uptake rate in the 'kit' group (17%) was significantly increased (RR=2.7, 1.0-7.2) in comparison to the control group.

Limitations

This defaulters list did not undergo any 'list cleaning' process to exclude screening ineligible women.

Methods

Defaulters aged between 56 and 60 years were identified from the Scottish Cervical Call-Recall System (SCCRS) in November 2012. I had the access to this database. A total of 649 defaulters were identified. One woman's address was not found and was excluded from the study. Remaining 648 defaulters were randomised into 3 arms using the www.statisticssolutions.net website. Controlled arm was consisted of 64 (10%) defaulters. The second and the third arms were consisted of 292 (45%) defaulters each. Controlled arm had no intervention. Whilst the second arm was sent the multiple options letter, the third arm was sent a self-sampling kit with the initial invitation letter. Screening status of women who were in the control arm and those who haven't had a self-sampling test were checked at 3 times points- 3, 6 and 12 months since the randomisation.

Results

Women who wished to self-collect had not been screened for varying duration of time. The median duration for which these 50 defaulters had not been screened (duration since the last smear test, if they had any or from 20 years of age) was 7.3 years and the median was 7 years with IQR of 4-10 years. Two (4%) of them had never been screened. There were 3 women on the non-routine recall category with a previous unsatisfactory smear. The duration since the last smear test of these 3 women was 2, 5 and 10 years.

Table 4.4.1: Response in the 'older' defaulter study at 6 months

Option		**Letter group (n=292)**		**Kit group (n=292)**		**Control group (n=64)**
		Ticked (%)	**Done (%)**	Ticked (%)	**Done (%)**	**Done (%)**
1	Smear at GP	15 (5%)	**9 (3%)**	6 (2%)	**4 (1%)**	**4 (6%)**
2	Smear-hospital clinic	4 (1%)	**4 (1%)**	3 (1%)	**2 (1%)**	**0**
3	HPV- hospital clinic	0 (0%)	**0 (0%)**	0 (0%)	**0 (0%)**	**0**
4	HPV- home	24 (8%)	**17 (6%)**	26 (9%)	**26 (9%)**	**0**
5	Want to discuss	1 (0%)	**0 (0%)**	1 (0%)	**1 (0%)**	**0**
6	Opt out	4 (1%)	**0 (0%)**	6 (2%)	**0 (0%)**	**0**
	Smear at GP without informing us	0 (0%)	**11 (4%)**	0 (0%)	**16 (5%)**	**0**
	Total positive response	44 (15%)	**41 (14%)**	36 (12%)	**49 (17%)**	**4 (6%)**

A total of 44 option lists were returned by women in the letter group (Table 4.4.1). The first option (to have a routine screening at the GP practice) was ticked by 15 (5%), the second (to be screened at a hospital clinic) was ticked by 4 (1%), the third (HPV testing at a hospital clinic) was ticked by 0 (0%), the fourth (HPV testing of a self-sample) by 24 (8%), the fifth (discuss) by 1 (0%) and the sixth (opt out) by 4 (1%). According to the number of option lists returned, the total positive response rate (excluding those who opted out) was 44 (15%). A total of 42 option lists were returned by women in the kit group. The first option (to have a routine screening at the GP practice) was ticked by 6 (2%), the second (to be screened at a hospital clinic) was ticked by 3 (1%), the third (HPV testing at a hospital clinic) was ticked by 0 (0%), the fourth (HPV testing of a self-sample) by 26 (9%), the fifth (discuss) by 1 (0%) and the sixth (opt out) by 6 (2%). According to the number of option lists returned, the total positive response rate (excluding

those who opted out) was 36 (12%). Four women (6.4%) in the control group have had smears in these 6 months.

We received 8 phone calls in relation to this study as they wanted to discuss and decide about their screening. Screening was not indicated for 4 of them, 3 decided to have a smear at GP and one has self-collected. If these 8 phone calls also counted under the option-5, the positive response rate would go up by another 1%.

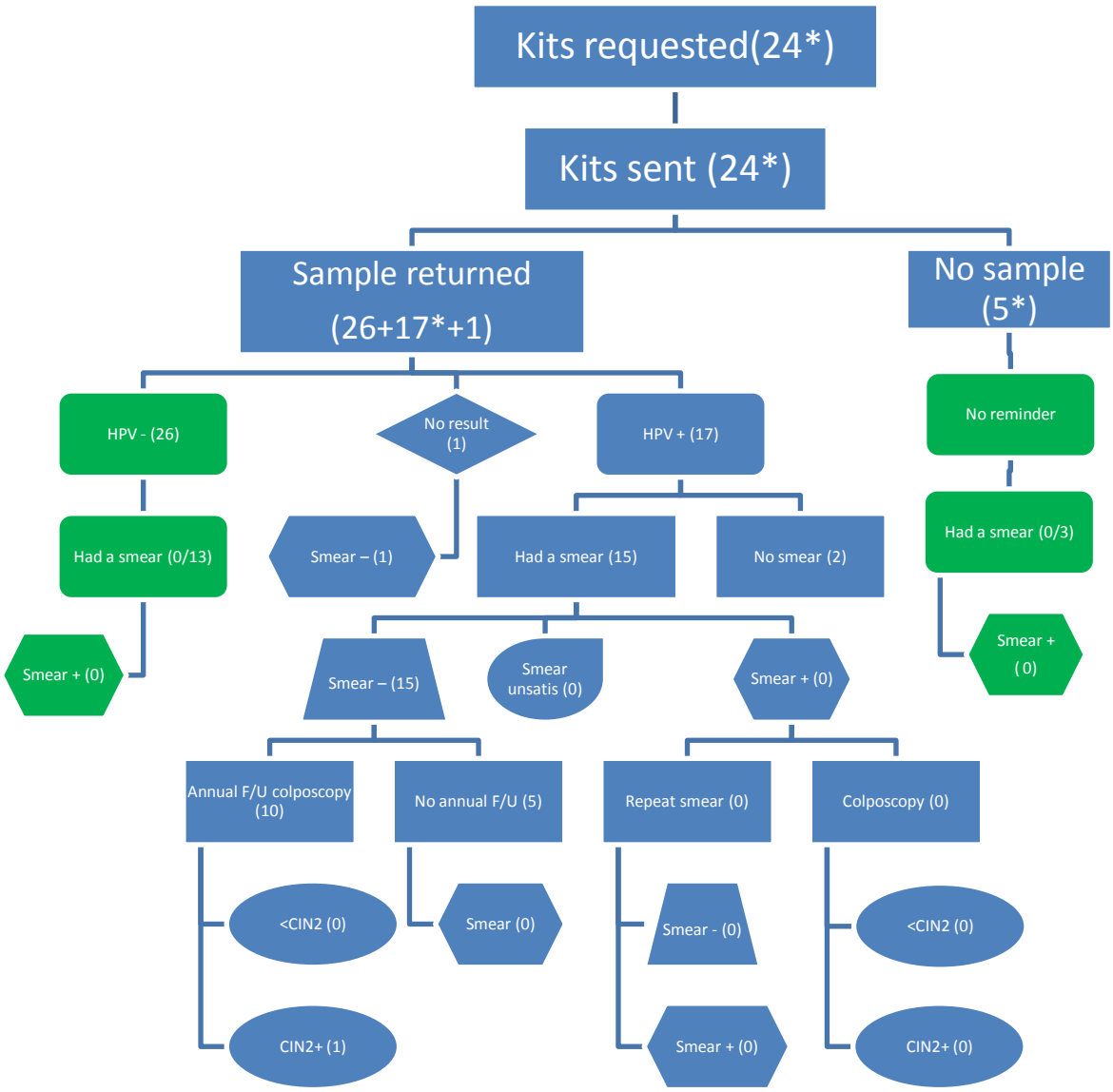
Among the women who opted out, 5/11 (45%) have had a total hysterectomy, 1 (9%) woman has had a cervical surgery, after which collecting smears was not apparently possible. Another woman was diagnosed with a stage 1b cervical cancer 2 years ago. Another 2 women had previous bad smear experiences and only one didn't give any reason.

All but one of the defaulters who asked for a hospital smear clinic have had smears, five at the hospital smear clinic, and one at the GP as she thought that the smear clinic would be at the Stranraer Hospital. She then, decided to go to local GP for a smear. The Galloway Community Hospital in Stranraer is located 73 miles west of Dumfries & Galloway Royal Infirmary, which takes 1h 40min to 2h journey.

Screening uptake rate in each arm of the trial has been measured at three time points, 3, 6 and 12 months. Please find the total combined screening uptake rates at 6 months in Fig 4.4.1.

Total screening uptake rate 3 months after randomisation was 39/292 (13.4%), 40/292 (13.7%) and 2/64 (3.1%) in the 'letter', 'kit' and the control group; respectively. Smear uptake rate 3 months after randomisation was 15/292 (5.1%), 14/292 (4.8%) and 2/64 (3.1%) in the 'letter', 'kit' and the control group; respectively.

Fig 4.4.1: Combined HPV screening data of both groups at 6 months



Abbreviations: HPV+= HPV positive; HPV-= HPV negative; smear+= smear positive; smear-= smear negative; <CIN2= low-grade CIN or less; CIN2+= high-grade CIN or worse; F/U= follow-up. *=number of samples received from the 'letter' group; the number of women is indicated within brackets.

Total screening uptake rate 6 months after randomisation was 41/292 (14.0%), 49/292 (16.7%) and 4/64 (6.2%) in the 'letter', 'kit' and the control group, respectively. Smear uptake rate 6 months after randomisation was 24/292 (8.2%), 22/292 (7.5%) and 4/64 (6.2%) in the 'letter', 'kit' and the control group, respectively. The total screening uptake rate of the interventional cohort at 6 months was 89/584 (15.2%).

Total screening uptake rate 12 months after randomisation was 57/292 (19.5%), 55/292 (18.8%) and 6/64 (9.4%) in the 'letter', 'kit' and the control group; respectively. Smear uptake rate 12 months after randomisation was 33/292 (11.3%), 29/292 (9.9%) and 6/64 (9.4%) in the 'letter', 'kit' and the control group; respectively.

Out of 50 women who wished to self-collect, 44 samples were received. One woman's sample was returned after the samples testing had ceased. She was offered a smear test which was been carried out in April 2013. The majority, 26/43= 60% were HPV negative, 40% were positive. A majority of HPV positives 15/17= 88% have had smear tests, all of them were negative.

Ten women had colposcopy and a cervical smear at the annual follow-up clinic (please see table 9.4 in Appendix 1). Colposcopic diagnosis was a high grade CIN in one case which was confirmed by biopsy as CIN2. All other colposcopies did not reveal any abnormality although one was unsatisfactory due to type 3 transformation zone. All cervical smears have been reported negative.

One woman who requested a self-sampling kit decided to have a smear test, which was carried out in January 2013. Of the 26 women who were tested negative for HPV, 13 were invited for a smear test from 1 January to 31 December 2013. None (0%) have had a smear test. Although 3 women in the group that did not return a sample (n=6) were called by SCCRS for a smear, none of them have had a smear test during the same period of time.

It was possible to check the screening status of each of these 648 defaulters. The relative screening uptake rates in each of these interventional arms in comparison to no intervention are presented in Fig 4.4.2a and Fig 4.4.2b.

Whilst 292 (45%) defaulters in the 'letter' arm were sent the multiple screening options letter, the defaulters in the 'kit' arm (n=292, 45%) were sent a self-sampling kit with the multiple screening options letter. No intervention was done for the 64 (10%) defaulters in the control arm (Fig 4.4.2a and Fig 4.4.2b). There were no 'list clearance' or 'reminder' interventions in this study.

Fig 4.4.2: Relative screening uptake in the older defaulter study

(a) between the self-sampling 'letter' and smear options against no intervention

Self-sampling 'letter' + smear options (intervention group)			No intervention (control group)		
Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate [% (95%CI)]**	Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate [% (95%CI)]**
41	292	**14 (10-19)**	4	64	**6 (2-13)**

(b) between the self-sampling 'kit' and smear options against no intervention

Self-sampling 'kit' + smear options (intervention group)			No intervention (control group)		
Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate [% (95%CI)]**	Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate [% (95%CI)]**
49	292	**17 (13-22)**	4	64	**6 (2-13)**

The relative increase in the positive response between the self-sampling and multiple smear options is presented in Fig 4.4.3 Defaulters in the 'kit + no reminder' study group were 2.7 (1.0-7.2) fold more likely to be screened in comparison to the no intervention arm. This difference is marginally statistically significant as the lower limit of the confidence interval is 1.005. Defaulters in the 'letter + no reminder' arm were 2.2 (0.8-6.0) folds more likely to be screened in comparison to the no intervention arm. This difference is not significant.

Fig 4.4.3: Analysis of the older defaulter study

	N screened	N not screened	Risk Ratio	95% Confidence Interval
control	4	60	1	reference
kit+ no reminder	49	243	2.685	(1.005, 7.173)
letter+ no reminder	41	251	2.247	(0.834, 6.048)

4.5 The younger defaulter study.

Study question

Can the screening participation be improved by sending multiple smear options letter to defaulters aged 20-29 years?

Summary answer

The multiple smear options letter has significantly increased the cervical smear uptake among defaulters in comparison to controls.

What is known and what this study adds

Offering more flexible screening options to defaulters does increase the screening participation. The screening uptake was significantly increased after the intervention of sending a multiple options letter. Only 27% of those who opted for a hospital smear test came to the hospital clinic. Whilst 66 informed us that they will have a smear at the GP, 194 had had a smear test at the community, indicating that sending a different letter to defaulters itself could be effective in raising the screening participation.

Limitations

Pre-intervention 'control' period could have been longer than 1-2 months. Many confounding factors may have contributed increasing the screening uptake by defaulters during the intervention period, such as the radio advertisement, social media and this study was preceded by other self-sampling studies in this small community etc. A formal randomisation may have strengthened the evidence developed.

Methods

We offered various opportunities to have a smear test to screening programme defaulters aged between 20 and 29 years.

We selected all under and unscreened women (defaulters) aged between 20 and 29 years, living in Dumfries & Galloway Health Board in August 2012 from the Scottish Cervical Call-Recall System (SCCRS) database (Fig 4.5.1). This database was generated at the end of August 2012. Addresses of all these women were cross-checked against the Sci Store Live database by the PI. A total of 1359 out of 1441 addresses were matched. These 1359

defaulters were contacted first. The remaining 82 were written to 2 months later. Eventually, all of these 1441 women were sent a letter (Fig 8.2.3, Appendix 2) inviting them to select one option from a list of six (Fig 4.5.2) (Fig 8.2.4, Appendix 2).

A list of 1441 defaulters was sent to the Principal Investigator on an Excel data sheet by the screening services manager. It was apparent on the Excel datasheet that these defaulters were listed according to their CHI numbers. A 10 digit CHI number begins with the date of birth followed by 4 random numbers. The database was arranged in the order of age in years. Women with the same year of birth were ordered according to the 4 digits at the end of the CHI number. Even rows of the Excel sheet were allocated to the Group A, odd rows were allocated to the Group B. There were 720 defaulters in Group A and 721 in Group B.

At the end of September, women in Group A were sent the standard screening letter with the standard cervical screening information leaflet, exactly the same as it would be sent by the Screening Services Department of NHS Dumfries & Galloway. Group B did not receive any intervention at the end of September. One month later, the screening status of all women in Group A and Group B were checked on the SCCRS and was recorded in the database. Women in both groups who hadn't had a smear test were sent the multiple options letter (Fig 8.2.3, Appendix 2) at the end of October. A radio advert was broadcast (on 14 days) in the 3rd and 4th weeks of October (Fig 4.5.1).

The multiple smear options letter was accompanied by a list of frequently asked questions about cervical screening (Fig 8.2.11, Appendix 2) and a pre-paid C5 size envelope addressed to the Screening Services Manager, NHS Dumfries and Galloway. There were two sheets in the letter. Returned letters were sorted and recorded by the Screening Services Manager's secretary and then passed on to the PI who facilitated the woman's choice. The Screening Services Manager dealt with opt outs and 'addressee left the area' replies.

In order to receive defaulters' requests, a secure email address (dg.smear@nhs.net) was generated by the IT Services Department, NHS Dumfries and Galloway, keeping with the local policy. A dedicated, password protected mobile phone with an activated tracker device was kept in the Ward 4 office to collect text messages from defaulters. The 'hotline' mobile phone contact number (07799 666 909) was displayed prominently in the letter.

Fig 4.5.1: Younger defaulter study flow chart

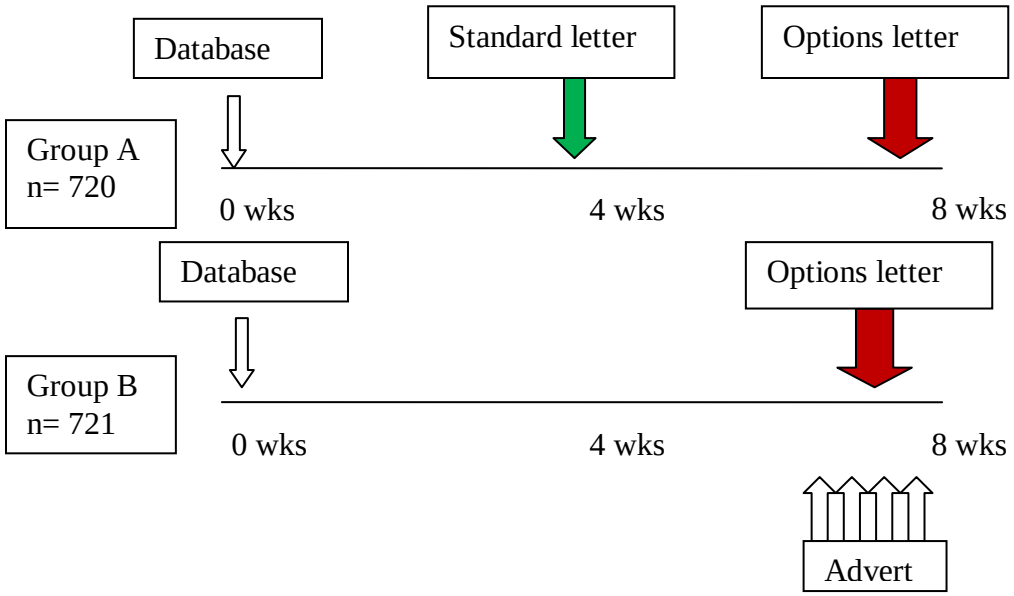


Fig 4.5.2: Options list 2 (smear option list): not including an option for self-sampling

Options List (please tick the most suitable one for you)

1. I will make an appointment with my GP Practice or the Sexual Health Clinic. ☐
2. Please give me an appointment at a hospital **evening** smear clinic. ☐
3. Please give me an appointment at a hospital **weekend** smear clinic. ☐
4. Please give me an appointment at a hospital **lunch time** smear clinic. ☐
5. I would like a doctor to contact me to discuss how I might get a test. ☐
6. None of above options suits me. ☐

Please tell us what arrangements might suit you or why you do not want a test

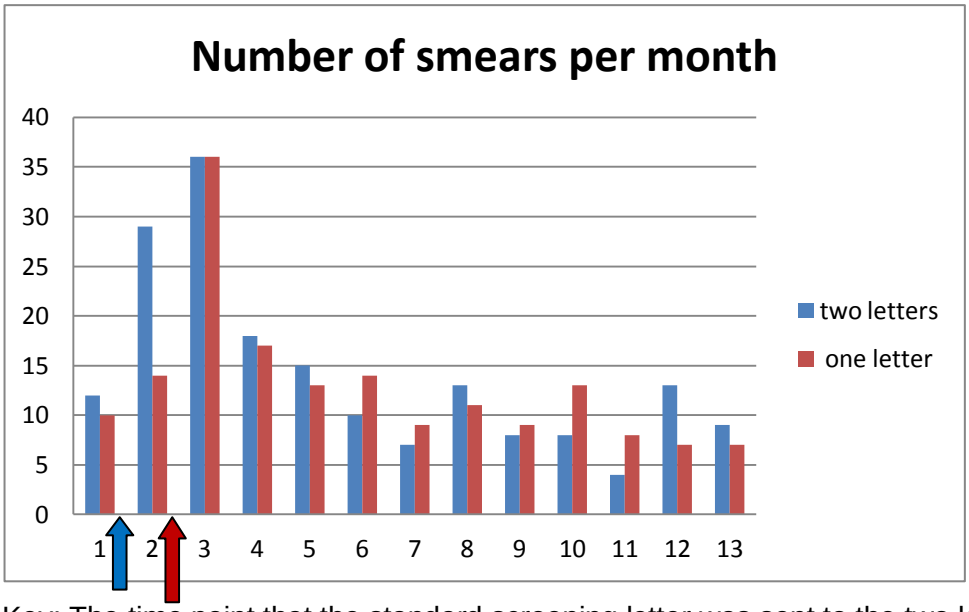
.....

Results

Whilst 12/720 (1.7%) women in the Group A (two letters group) have been to a smear test; 10/721 (1.4%) in Group B (one letter group) have had a smear test by the 30th of September.

A sharp rise of smear uptake per month was seen in the 2nd to 4th months (Fig 4.6.3). The same trend is seen here as well as the two letters group. In the one letter group, where the intervention was carried out at the end of the 2nd month, a sharp rise is seen from the 3rd to 5th months (Table 4.5.1). A total of 218 smears were carried out in the intervention period of 6 months.

Fig 4.5.3: Number of smear tests per month in one (n=721) and two (n=720) letters groups



Key: The time point that the standard screening letter was sent to the two letters group is maked with a shorter, blue arrow. The time point that the mutiple smear options letter was sent to both groups is marked with a longer, red arrow.

The cumulative smear uptake, rate 6 months after the intervention (circled in Table 4.5.1) in the Group A was 115/720= 16.0% and 100/721= 13.9% in group B. Hence, the total cumulative smear uptake rate at 6 months after the intervention in this cohort was 218/1441= 15.1%. The cumulative smear uptake rate of the control (no intervention) group of the older (56-60 years) defaulter's study was 4/64= 6.2%.

Over the seven months either before the intervention or more than 6 months after the intervention 135 (of 1441) women were screening, corresponding to 1.34% per month. Over the six months following the intervention 225 were screened corresponding to 2.6% per month. Thus over six months an extra 7.6% of women were screened.

Table 4.5.1: Smear uptake per each month in the 'younger' defaulter study

month	total	two letters	one letter
1 (Sep 2012)	22	12	10
2 (Oct 2012)	43	29	14
3 (Nov 2012)	72	36	36
4 (Dec 2012)	35	18	17
5 (Jan 2013)	28	15	13
6 (Feb 2013)	24	10	14
7 (Mar 2013)	16	7	9
8 (Apr 2013)	24	13	11
9 (May 2013)	17	8	9
10 (Jun 2013)	21	8	13
11 (Jul 2013)	12	4	8
12 (Aug 2013)	20	13	7
13 (Sep 2013)	16	9	7
total	**350**	**182**	**168**

Key: Considering circled six months as the intervention and remaining 6-7 months as the control. The intervention began at the end of month 1 in the 'two letters' group (A). It began at the end of the month 2 in the 'one letter' group (B).

Please see the Table 4.5.2 for the response rate and screening status at 2, 6 and 12 months since the first intervention (end of Sep 2012). At the end of the 2nd month (on 30 Nov 2012), the total positive response rate was 8% (112/1359). At the end of the 6th month (on 31 Mar 2013), the total positive response rate was 10% (133/1441).

Eighty two addresses which did not match when cross-checked against the Sci Store Live database were recruited after one month (end of October). A small proportion (3/82= 4%) of women have positively responded at the end of 6 months.

Table 4.5.2: Results of younger defaulters study at 2, 6 and 12 months (N=1441)

		2 months		6 months		12 months	
Option		Wished (%)	**Actually smeared (%)**	Wished (%)	**Actually smeared (%)**	Wished (%)	**Actually smeared (%)**
1	Smear at GP	55 (4)	**13 (1)**	66 (5)	**33 (2)**	66 (5)	**43 (3)**
2	Smear at hospital **evening** clinic	24 (2)	**8 (1)**	26 (2)	**10 (1)**	26 (2)	**12 (1)**
3	Smear at hospital **weekend** clinic	18 (1)	**5 (0)**	23 (2)	**6 (0)**	23 (2)	**8 (0)**
4	Smear at hospital **lunch time** clinic	12 (1)	**4 (0)**	15 (1)	**5 (0)**	15 (1)	**6 (0)**
5	Wanted to discuss	3 (0)	**0 (0)**	3 (0)	**0 (0)**	3 (0)	**0 (0)**
6	Opt out	39 (3)	**0 (3)**	49 (3)	**0 (0)**	49 (3)	**0 (0)**
	Smear at GP w/o informing us		**92 (7)**		**164 (11)**		**281 (20)**
	Total positive response	112 (8)	**122 (8)**	133 (10)	**218 (15)**	133 (10)	**350 (24)**

Six months after the first intervention, option 1 (smear at GP) was selected by 66 women, option 2 (evening hospital clinic) was selected by 26, option 3 (weekend hospital clinic) was selected by 23, option 4 (lunch time hospital clinic) was selected by 15 and option 5 (wanted to discuss) was selected by 3. The screening services manager and the principal investigator received 10 phone calls, 3 emails, 2 text messages and 2 letters to discuss screening options from this cohort of 1441 younger defaulters. It appeared that 164 women who never replied to our correspondence have had smears at the community. However, a good proportion of these defaulters might have had smears regardless of our letter/s.

On 30 September 2013 (12 months after the first intervention), about a quarter 350/1441 (24.3%) of these younger defaulters have had smears. Nineteen (19/350=5.4%) smears were abnormal. Of the 19 abnormal smears, 11 (58%) smears had a high grade abnormality. There were 16 colposcopy referrals. All referred women attended the colposcopy clinic. Eleven (3%) high grade CIN (CIN2+) were diagnosed in this younger cohort of 350 defaulters. Please find these results in Table 4.5.3.

Table 4.5.3: Results and diagnosis of not-normal results of 350 smears

Smear abnormality	n	Number of women referred to colposcopy	Number of histological diagnosis
Unsatisfactory	4	0	0
Borderline	3	0	0
Mild (low-grade)	5	1	1x CIN2
Moderate (HG- moderate)	5	5	2x CIN2 3x CIN3
Severe (HG-severe)	5	5	1x CIN1 2x CIN2 2x CIN3
Glandular abnormality	1	1	1x CGIN
Invasion	0	0	0
Total	**23**	**16**	**11xCIN2+**

Assessment of the relative effectiveness of interventions of the 'younger' defaulter study was carried out by comparing the first 6 months following the intervention (intervention period) to the months before and after this time (control period). Whilst the two letters group was not intervened in the first month, one letter group was not intervened in the first 2 months. These 1-2 months along with the remaining 4-5 months after the end of the intervention period (6 months in total) were considered as the 'control' period (Table 4.5.1). Note that month 13 data are not considered in this analysis in order to have 6 months in both the intervention and the control periods.

Whilst 12/720 (1.7%) women in the two letters group (A) have had a smear test prior to the intervention; 24/721 (3.3% in two months) in the one letter group (B) have had a smear test prior to the intervention. A sharp rise of smear uptake per month is seen in the first 2 months after the intervention in both groups. The cumulative smear uptake rate in the intervention period in the two letters group (A) was 115/720= 16.0% and 100/721= 13.9% in the one letter group (B). Whilst 46 smear tests were carried out from the months 8 to 12 in the two letters group (A), 37 smear tests were carried out from the months 9 to 12 in the one letter (B) group, after the end of the intervention period which was considered as the 'control' period. (Fig 4.5.4a and Fig 4.5.4b).

Fig 4.5.4: The relative screening uptake in 'younger' defaulter study

(a) The screening uptake between the two letters group (A) against no intervention

Two letters group (A) (cases)			No new intervention (control)		
Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate per 6 months [% (95%CI)]**	Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate per 6 months [% (95%CI)]**
115	720	**16 (13-19)**	58	720	**8 (6-11)**

(b) The screening uptake between the one letter group (B) against no intervention

Two letters group (B) (cases)			No new intervention (control)		
Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate per 6 months [% (95%CI)]**	Number of defaulters screened (n)	Total number of participants (N)	**Screening uptake rate per 6 months [% (95%CI)]**
100	721	**14 (11-17)**	61	721	**8 (6-11)**

Defaulters in the two letters intervention group were 2.0 (1.5-2.7) fold more likely to be screened than its control group. This difference is statistically significant. Defaulters in the one letter intervention group were 1.6 (1.2-2.2) fold more likely to be screened than its control group. This difference is statistically significant.

In order to further analyse the relative effectiveness of the younger defaulter study which offered multiple smear options, data from a historical control group was also used. A new list of defaulters aged between 21 and 30 years was generated on 27 September 2013, one year after recruiting women to the younger defaulter study. Their screening status was checked on 28 March 2014. Of the women who have had a smear test, duration from the last screening recall (reminder) letter to the current smear test was recorded.

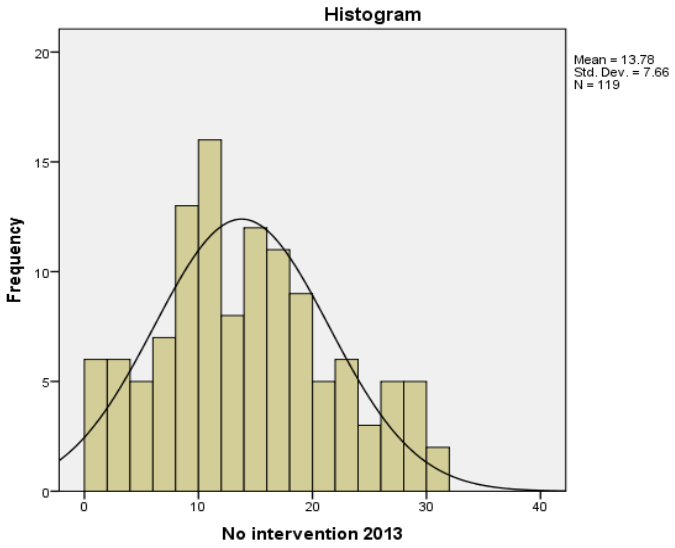
The mean age of the historical control group (N=1732) was 25 years with SD of 3 years. A total of 119 smears (6.9% of the group had a smear) were carried out in 6 months. Number of smears carried out in each month from October 2013 to March 2014 was 17, 18, 13, 20, 27 and 24 (Fig 4.5.5).

Fig 4.5.5: Number of smears per month in the historical control group

Month	Smears per month
1 (Oct 2013)	17
1 (Nov 2013)	18
3 (Dec 2013)	13
4 (Jan 2014)	20
5 (Feb 2014)	27
6 (Mar 2014)	24
Total (6 months)	119

The time interval between the last screening recall letter to the smear test (letter to smear interval) of these 119 smears is illustrated in Fig 4.5.6. The mean letter to smear interval is 14 months with SD of 8 months.

Fig 4.5.6: The last screening recall letter to the smear test (letter to smear interval in months)

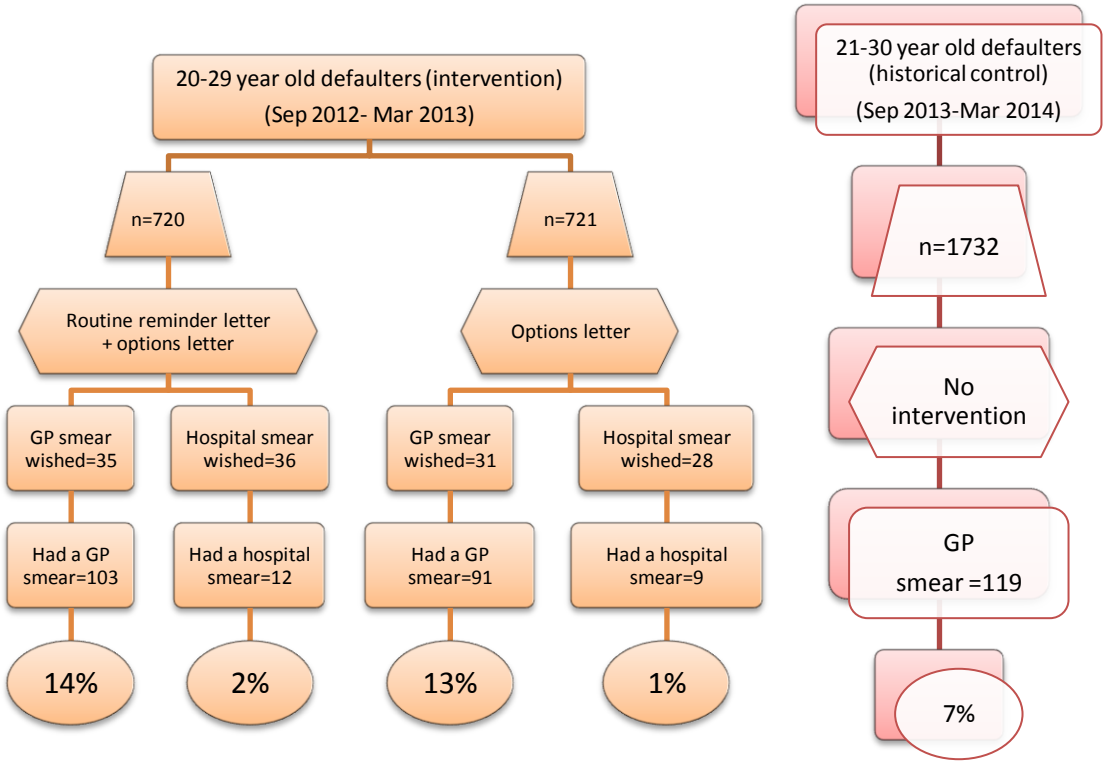


If this historical group was considered as the control group of the one letter group of the younger defaulter study (who received a multiple smear options letter), the risk ratio of the smear uptake can be calculated. A total of 66 women ticked the option-1 indicating that they wish to have a smear at the GP practice. A similar number of women wished to have a hospital smear. However, only about a third (21/64=33%) came to the hospital smear clinic. Although 66 women informed us that they will have a smear at the GP, 194 have been to a smear test by 6 months. This indicates that the hospital smear clinic didn't play a big role in increasing the smear uptake rate. A total of 115 (16%) in the 2 letters group 100 (14%) in the one letter group and 119 (7%)

in the historical control group and 119 (8%) in the two contemporaneous control groups had smears in 6 months (Fig 4.5.7). The smear uptake rate at 6 months in the interventional group was roughly twice as high as in the historical control group (n=1732). This difference was more clearly seen at 3 months where 66/721 in the one letter group and 48/1732 have had smears (RR=3.3, 2.3-4.7).

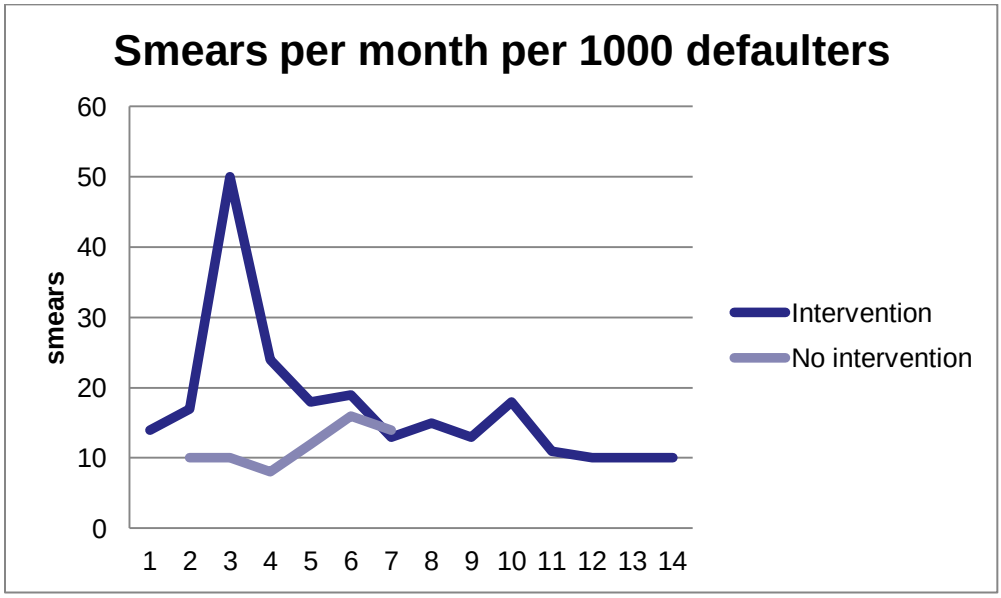
The defaulter's response in the younger defaulters study was quicker than other studies. Whilst a vast majority (122/133=92%) responded within 2 months, 11 women responded in the third month. Therefore, the screening uptake rate at 3 months was calculated. A total of 66 defaulters in the one letter group (n=721) had smears in 3 months. In comparison, 48/1732 defaulters in the historical control group had smears in 3 months. At 3 months, the smear uptake rate of the one letter group was 3.3 (2.3-4.7) times higher than the historical control group, which is statistically significant.

Fig 4.5.7: Screening summary of 'younger' defaulter study at 6 months



Trends in seen in the smear uptake rates between the one letter group and the historical control group are illustrated in Fig 4.5.8. Intervention was carried out at the end of the second month.

Fig 4.5.8: Trends seen in smear uptake rates per 1000 defaulters



4.6 Annual follow-up of vaginal HPV positives.

Methods

All women testing positive for HPV on a self-collected sample were invited for clinician sampling in a hospital clinic in 2012. Those who attended had a liquid based sample collected which was used for both cytology and HPV testing (the smear residual was tested for HPV).

All women who have had a positive vaginal HPV test; except the ones that were referred to colposcopy with an abnormal smear test, were invited for an annual follow-up clinic in 2013. These annual follow-up clinics were run by the PI who is a British Society of Colposcopy and Cervical Pathology Society's (BSCCP) accredited colposcopist. The PI was assisted by a female Gynaecology/ Colposcopy Nurse Specialist.

Participants were appropriately counselled and informed written consent was obtained for a cervical smear sample and for diagnostic colposcopy ±biopsy. After collecting the cervical

cytology (smear) sample using 2 brushes (Cervex brush and endocervical brush), a diagnostic colposcopy was performed according to the BSCCP standards (NHSCSP 2010). All acetowhite areas suggestive of CIN were biopsied.

All biopsy positive for CIN1+ were referred to the Clinical Supervisor, Dr Heather Currie's colposcopy clinic for further assessment and/or treatment.

These follow-up colposcopy clinics were run from 18 June 2013 to 31 December 2013. Cytology, colposcopy and histology results were recorded and correlated.

Results

Sixty seven women attended the annual follow-up clinic. Colposcopic findings of each of these vaginal HPV positive women with a lesion are presented in the Fig 8.1.5 in the Appendix 1. Please find the analysis of these lesions in the section 4.7.

About 30 women did not attend the annual follow-up clinic. Six women were unable to come due to the distance (60-70 miles from Dumfries hospital). They were happy with the reassurance they got from the last smear test. They were advised to attend their future smears, regularly. One person has had a total abdominal hysterectomy in April 2013. One person is currently undergoing breast cancer treatment. One person informed that she is currently pregnant. One person has severe motion sickness so would rather not travel from Stranraer (73 miles). One busy healthcare professional has been sick and never attended both appointments.

Two persons could not attend the clinic as the follow-up (colposcopy) clinics were not run in evenings. One defaulter didn't come this time as her last smear test that she has had at the hospital smear clinic was painful. Two persons opted out by sending emails, but not reason was stated. All other women did not attend without giving any reasons.

4.7 Analysis

Response rates

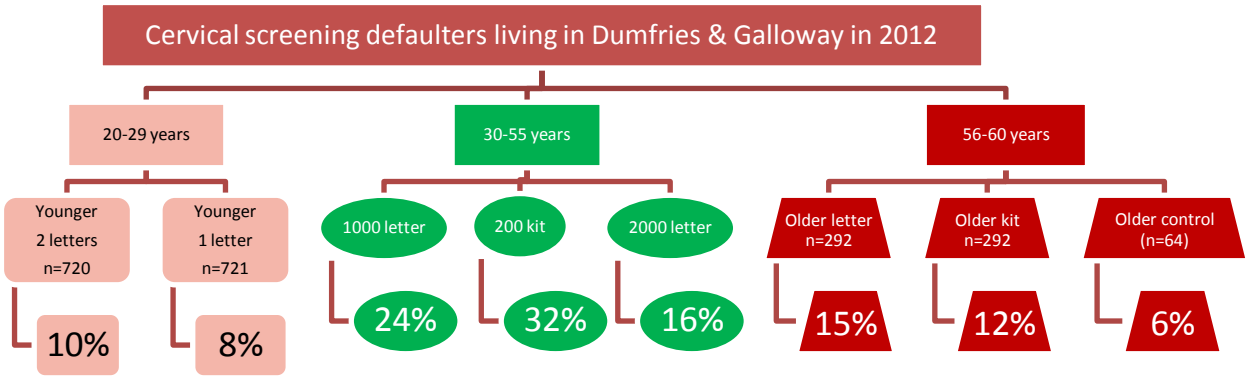
The total response for each study group at 6 months is presented in Table 4.7.1 and Fig 4.7.1.

Table 4.7.1: Screening data of all defaulters at 6 months

Outcome at 6 months	1000 study (letter)		200 study (kit)		2000 study (letter)		Older study (letter)		Older study (kit)		Younger study (2 letters)		Younger study (1 letter)		Control (none)	
n	**1000**	**%**	**200**	**%**	**2031**	**%**	**292**	**%**	**292**	**%**	**720**	**%**	**721**	**%**	**64**	**%**
Age range	30-55		30-55		30-55		56-60		56-60		20-29		20-29		56-60	
Mean age (SD)	43 (7.5)		43 (7.7)		43 (7.5)		58 (1.4)		58 (1.4)		24 (2.7)		24 (2.7)		58 (1.4)	
Smear GP	63	6	8	4	108	5	15	5	6	2	35	5	31	4	4	6
Sm. hosp	23	2	5	3	40	2	4	1	3	1	38	5	29	4	-	-
HPV hosp	5	1	0	0	3	0	0	0	0	0	-	-	-	-	-	-
HPV home	129	13	46	23	158	8	24	8	26	9	-	-	-	-	-	-
Discuss	16	2	4	2	16	0	1	0	1	0	2	0	1	0	-	-
Positive response	**236**	**24**	**63**	**32**	**325**	**16**	**44**	**15**	**36**	**12**	**73**	**10**	**60**	**8**	**4**	**6**
95%CI		**21-26**		**25-38**		**14-18**		**11-20**		**9-17**		**8-13**		**6-11**		
Actual screened	**232***	**23***	**61***	**31***	**342***	**17***	**41**	**14**	**49**	**17**	**115**	**16**	**100**	**14**	**4**	**6**
95%CI								**10-19**		**13-22**		**13-19**		**11-17**		**2-13**
Opt out	22	2	3	2	46	2	4	1	6	2	27	4	22	3	-	-

*estimated figures based on the sensitivity analysis (Table 4.7.3)

Fig 4.7.1: Positive response rates of all defaulters at 6 months



The positive response rate of each study group is presented in Table 4.7.1. The positive response percentage (rate) and the 95% confidence interval of the 1000 letter + reminder study group was 23.6% (21-26), of the 200 kit + reminder study group was 31.5 (25-38), of the 2000 letter + reminder study group was 15.8 (14-18), Older letter + no reminder study group was 15.1 (11-20), Older kit + no reminder study group was 12. (9-17), Younger 2 letters study group was 10.1 (8-13) and Younger 1 letter study group was 8.3 (6-11).

The total screening uptake rate at 6 months is known in the Older and Younger defaulter studies. It was 14 (10-19) in the Older letter + no reminder study group, 17 (13-22) in the Older kit + no reminder study group, 16 (13-19) in the Younger 2 letters study group and 14 (11-17) in the Younger 1 letter study group. Four defaulters in the non-intervention arm of the 'older' control group have had smears in 6 months, making the screening uptake rate of 6.3% (2-14).

The 1000, 200 and 2000 defaulter studies

Defaulters aged between 30 and 55 years were offered self-sampling, in addition to multiple smear options. Data relating to the total number of self-samples returned between the self-sampling letter + reminder group versus the self-sampling kit + reminder group is presented in Fig 4.7.2. A total of 3031 participants were sent a letter and a reminder, 200 participants were sent a self-sampling kit and a reminder. Whilst 200 samples were returned in the letter+ reminder group, 40 samples were returned in the kit + reminder group.

Fig 4.7.2: The relative self-sampling uptake rate between the ‘letter’ and the ‘kit’ method.

Self-sampling ‘letter’ + reminder (intervention 1)			Self-sampling ‘kit’ + reminder (intervention 2)		
Self-samples returned (n)	Total number of participants (N)	**Returns rate [% (95%CI)]**	Self-samples returned (n)	Total number of participants (N)	**Returns rate [% (95%CI)]**
200	3031	**7 (6-8)**	40	200	**20 (16-23)**

Participants in the self-sampling kit + reminder group were 3.5 (2.4-5.1) fold more likely to return a self-collected sample than the self-sampling letter + reminder group. This difference is statistically significant ($p<0.001$). Note however that the difference in the Older women study between women sent a kit initially and those who had to request one was relatively much less. Overall the screening uptake rates were 49/292 compared with 41/292: an additional 3% were screened risk ratio 1.20.

Age related trends seen in the 30-55 year age gruop

Potential age related trends in relation to the positive response rate, choosing to self-sample (option 4) or choosing to have a smear at the GP (option 1) have been examined in 1000, 200 and 2000 study groups (Table 4.7.2). Respondents were divided into 3 age groups 30-38, 39-47 and 48-55. The positive response rate remained similar across all 3 age groups in all 3 study groups with no statistically significant difference. The probability of choosing self-sampling remained similar across all 3 age groups in all 3 study groups with no statistically significant difference. The probability of choosing to have a smear test at the GP remained similar across all 3 age groups in all 3 study groups with no statistically significant difference.

Table 4.7.2: Age related trends in choosing different options- n (%) and 95%CI of the %

	1000 defaulters - letter				200 defaulters - kit				2000 defaulters - letter			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Option 1	63	63	49	80	8	4	2	8	105	5	4	6
Option 2	23	23	15	34	5	3	1	6	39	2	1	3
Option 3	5	5	0	12	0	0	0	2	3	0	0	0
Option 4	129	13	11	15	46	23	17	30	158	8	7	9
Option 5	16	2	1	3	4	2	1	5	16	1	0	0
Option 6	22	2	1	3	3	2	0	4	46	2	2	3
Positive response	236	23.6	21.0	26.4	63	31.5	25.1	38.4	321	15.8	14.4	17.7
Sample received	92	9.2	7.5	11.2	40	20.0	14.7	26.2	108	5.3	4.4	6.4
Positive response												
Age 30-38	80	23	19	28	22	31	21	44	104	15	13	18
Age 39-47	81	24	20	29	20	34	22	48	112	17	14	20
Age 48-55	75	24	19	29	21	29	19	41	105	15	13	18
Option 4												
Age 30-38	40	12	8	15	15	21	12	33	49	7	5	9
Age 39-47	45	13	10	18	15	26	15	39	59	9	7	11
Age 48-55	44	14	10	18	16	22	13	34	50	7	5	11
Option 1												
Age 30-38	23	7	4	10	3	4	1	12	40	6	4	8
Age 39-47	22	7	4	10	2	3	0	12	30	5	3	6
Age 48-55	18	6	3	9	3	4	1	12	36	5	4	7

Abbreviations: Propor= proportion

Sensitivity analysis

Whilst some defaulters who wished to have smear test were never able to do it, others who didn't let us know their intentions have had it. It was not possible to check the screening status of those who did not let us know their screening intentions in the 30-55 year old cohort of defaulters. In the 'Younger' defaulter study, although 130 out of 1441 defaulters informed us that they wish to have a smear test, 218 have actually had smears at 6 months. Similarly, in the 'Older' defaulter study, although 28 out of 584 defaulters informed us that they wish to have a smear test, 47 have actually had smears at 6 months. Based on these figures, the smear uptake rates were estimated for the 30-55 year age group (Table 4.7.3).

Table 4.7.3: Actual and estimated smear uptake at 6 months among defaulters who wished to have a smear (sensitivity analysis)

	Study group (method of intervention)	n/N (%) who wished to have a smear	n/N (%) who actually had a smear	n/N (%) estimated smear uptake
1	1000 (letter+remind)	86/1000 (9%)	?	140/1000 (14%)
2	200 (kit+remind)	13/200 (7%)	?	21/200 (11%)
3	2000 (letter+remind)	148/2031 (7%)	?	234/2031 (12%)
4	'Older' letter+ no remind	19/292 (7%)	24/292 (8%)	n/a
5	'Older' kit+no remind	9/292 (3%)	23/292 (8%)	n/a
6	'Younger' 2 letters	73/720 (10%)	115/720 (16%)	n/a
7	'Younger' 1 letter	60/721 (8%)	100/721 (14%)	n/a
	Total	**408/5256 (8%)**	**264/2025 (13%)**	**405/3231 (13%)**

The total screening uptake rate in the 1000, 200 and 2000 studies can be estimated using these estimated smear uptake numbers, as checking their screening status was not possible. It would be (92+140)/1000= 24% in the 1000 defaulter study. It would be (40+21)/200= 31% in the 200 defaulter study. It would be (107+234)/2031= 17% in the 2000 defaulter study. The total screening uptake rate in the older defaulter study is 15% and the younger defaulter is 15%. The estimated total screening uptake rates appear similar to the total positive response rate in the 1000, 200 and 2000 study groups. Therefore, it is reasonable to conclude that trends seen in positive response rates in the 1000, 200 and 2000 study groups are comparable to the estimated screening uptake rates.

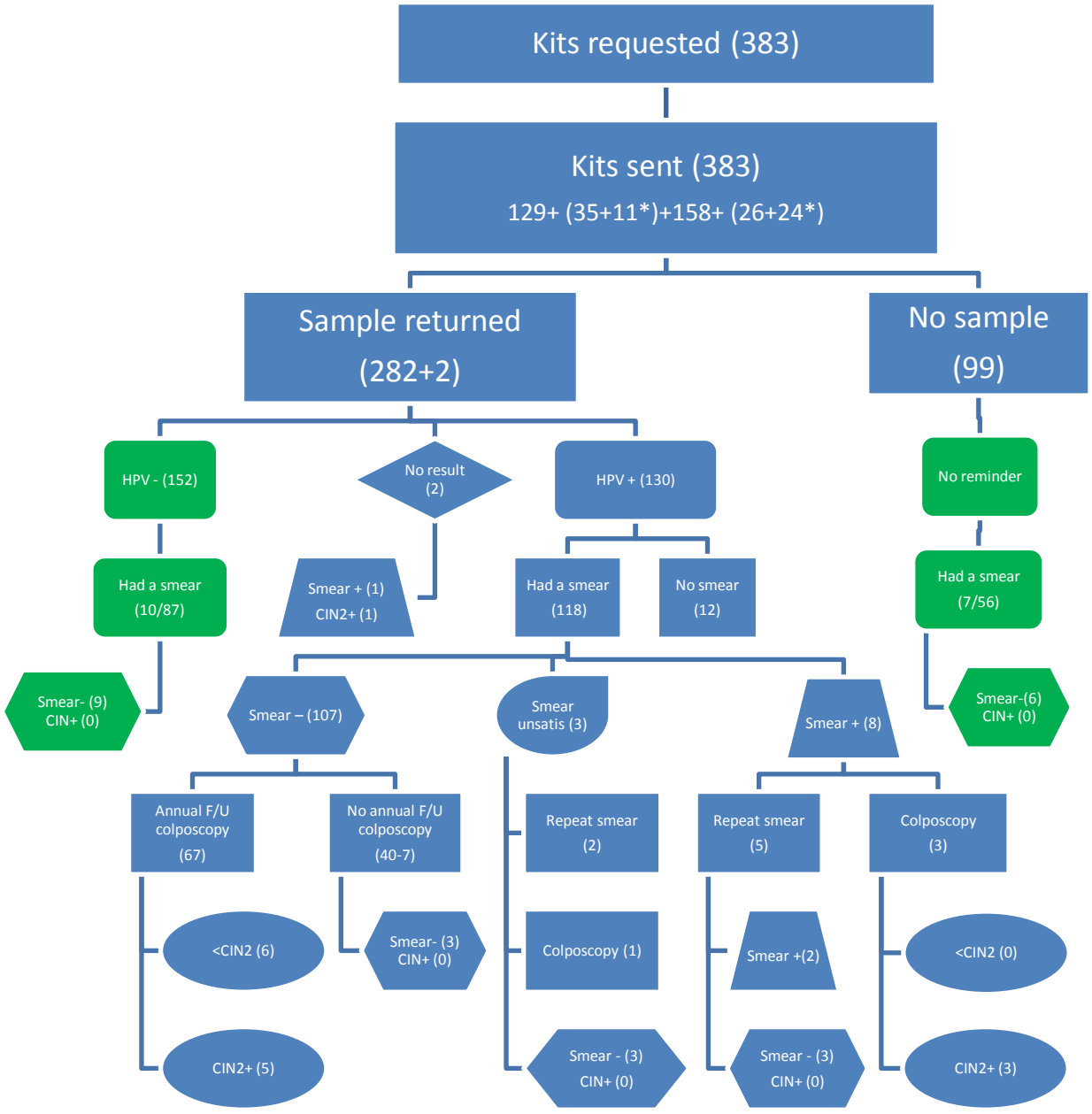
The sum of the estimated and actual number of smears carried out in defaulters who did not do HPV screening was 669. Furthermore, a total of 137 defaulters who wished to self-collect (118xHPV+, 10xHPV-, 2xNo HPV result, 7xNo sample) have had smears (Table 4.7.3). This indicates that about 800 defaulters may have had smears during the study period.

HPV screening

A condensed summary of defaulters who wished to self-sample is presented in the Fig 4.7.3. A total of 322 primary kit requests have been received. Sixty one kits were retuned with a sample by women in study groups who received a kit with the initial invitation (n=200+292=492). A total of 284 samples were returned by women although a sample was returned after the HPV testing has ceased and one was lost. These two women had no HPV result. Both of them were offered a hospital smear appointment. One of them had a high-grade smear and hgCIN. A small proportion 3/282 (1%) of samples didn't give a valid HPV results in the first run due to problems in the internal control, but all of these 3 gave a valid result in the second run. Whilst 152 (54%) were HPV negative, 130 (46%) were HPV positive.

A vast majority (118/292=91%) of HPV positives have had smears. Eight (6.8%) were positive, 107 (90.7%) were negative and 3 (2.5%) smears were unsatisfactory (inadequate sample). Of 8 abnormal smears, 3 met the criteria for colposcopy referral. All of these 3 were diagnosed to have CIN3. Repeat smears were indicated for other 5 abnormal smears. All of these 5 women had smears, 3 were and 2 were abnormal. Both of these women were referred to colposcopy. Whilst one of them had CIN1, the other woman did not attend. Colposcopy was indicated for one of the 3 women who had unsatisfactory smear result due to 3 consecutive unsatisfactory results. She was diagnosed to have vaginal atrophy. All 3 women with unsatisfactory smears had subsequently had negative smears. The majority (67/107=62.6%) of smear negatives (but vaginal HPV positives), came to the annual follow-up clinic. Whilst 7 women opted out giving reasons, 33 women did not attend. Of 67 women who had a repeat smear test and colposcopy approximately 1 year (range 11-14 months, median=mode= 12 months) after they collected the vaginal sample. Tissue diagnosis was available for 17/67 colposcopies carried out. There were 6xCIN1 and 5xCIN2 out of which only 3 had an abnormal smear in 2013 (Fig 4.7.3).

Fig 4.7.3: HPV screening and follow-up data of the whole 30-60 year old defaulters

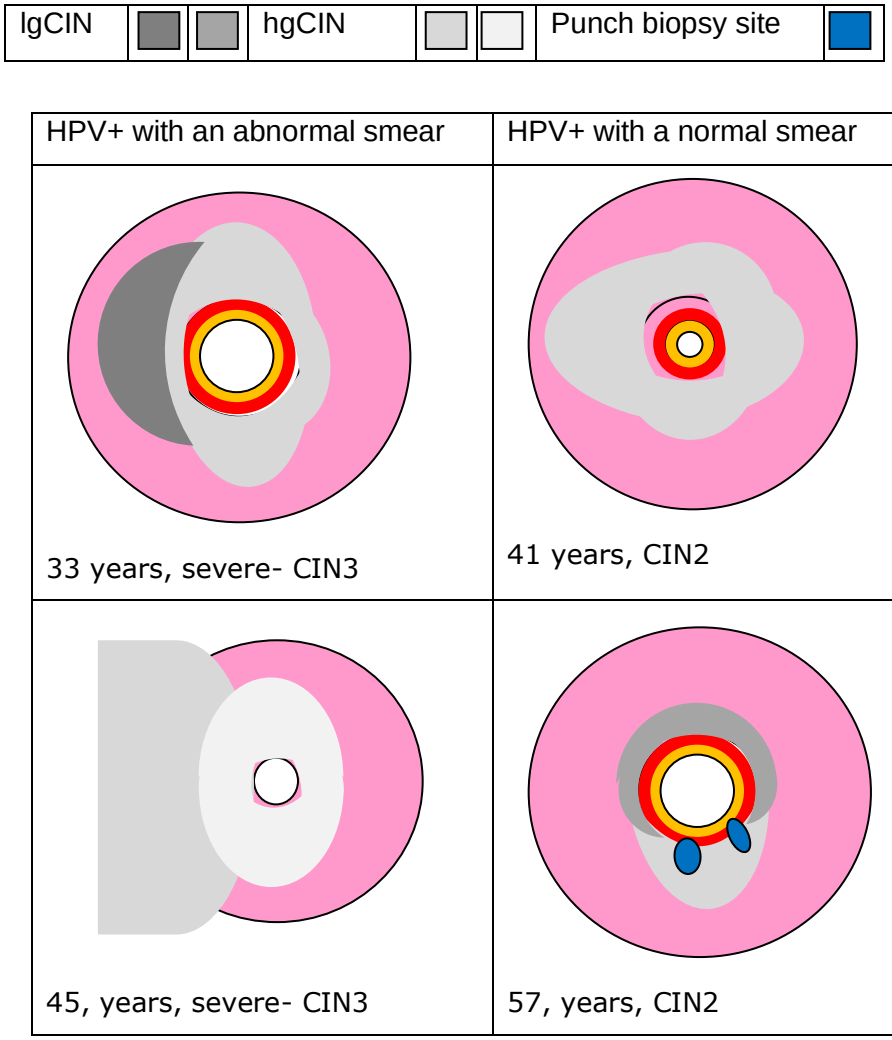


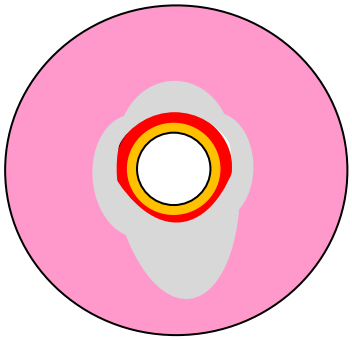
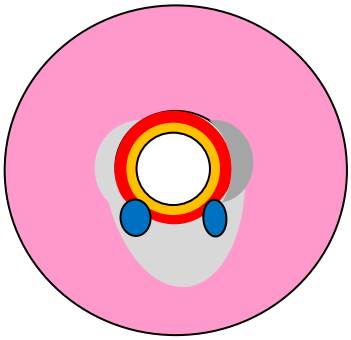
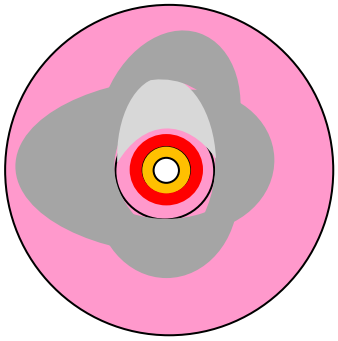
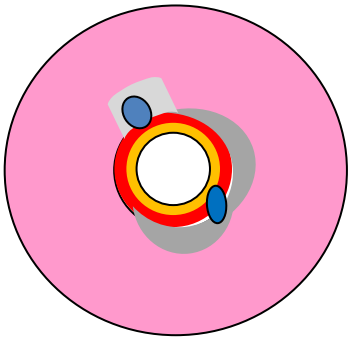
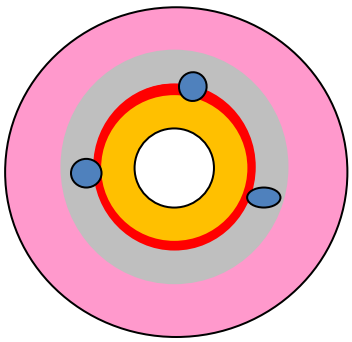
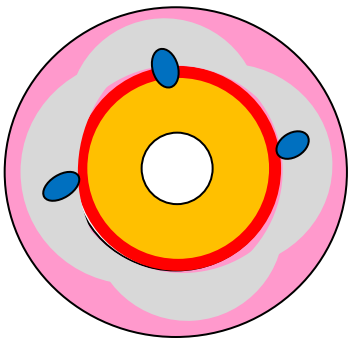
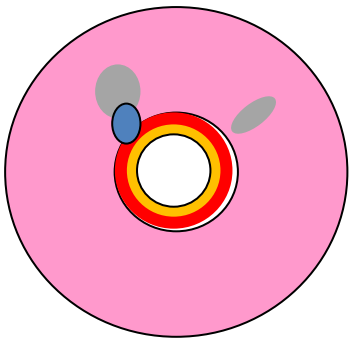
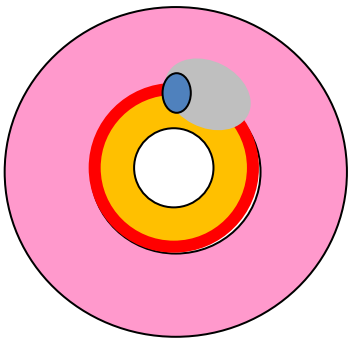
Abbreviations: *Women who ticked option-4 only after receiving the reminder letter were sent a second kit; HPV+= HPV positive; HPV-= HPV negative; smear+= smear positive; smear-= smear negative; <CIN2= low-grade CIN or less; CIN2+= high-grade CIN or worse; F/U= follow-up. The number of women is indicated within brackets.

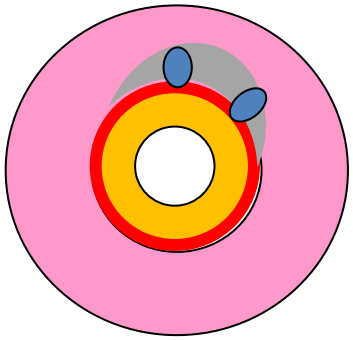
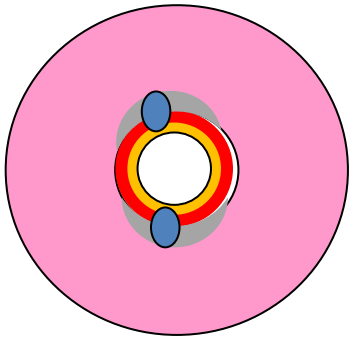
Diagnostic outcomes of HPV screening

Histological diagnosis of a cervical lesion is considered to be the gold standard. However, the natural histories of two different CIN2 can take two different pathways; whilst one may spontaneously regress, other may develop into a carcinoma, which will be hard to predict. The extent to which these neoplastic lesions affect the cervix should be one such surrogate marker, which at least indicates the severity of HPV disease on the cervix. Comparison of colpographs between the lesions diagnosed by HPV screening alone versus lesions diagnosed after an abnormal smear test following HPV screening (Fig 4.7.4) would give us some clue regarding their clinical relevance. Lesions spread extensively tend to have more clinical significance than small focal lesions, although they have the same histological diagnosis.

Fig 4.7.4: Comparison of colposcopy findings of cytology detected lesions versus those were not



 44 years , severe- CIN2	 41 years, CIN2
 51 years, moderate- CIN2	 45, years, CIN2
 30 years, bnc- CIN1	 39, years, CIN1
 46 years, bnc-CIN1	 32 years, CIN1

	 49 years, CIN1
	 55 years, CIN1
n=6 (2xCIN3, 2xCIN2, 2xCIN1)	n=8 (0xCIN3, 4xCIN2, 4xCIN1)

It appears that lesions associated with abnormal cervical cytology in these 14 CIN diagnosed in 30-60 year old age group are generally larger than their HPV-only counterparts.

CHAPTER 5

Other research to complement interventional studies

5.1 Trends seen in colposcopy referrals during the study period

Study question

Were more defaulters referred to colposcopy during the study period when multiple screening options had been offered to them?

Summary answer

The number of new defaulters referred to colposcopy was significantly increased by three fold in during June-December 2012, in comparison to the same time period in 2011. Consequently, 15 extra cases of CIN2 or worse were diagnosed in 2012.

What is known and what this body adds

It is difficult to measure the real impact of our study on cervical screening outcomes. The number of new defaulters referred to colposcopy was significantly increased during June-December 2012, in comparison to the same time period in 2011. Our study may have contributed to bringing significantly more defaulters back to screening in the last 7 months in 2012 in comparison to the same period in 2011.

Limitations

Screening outcomes (diagnoses) of all new colposcopy referrals were not assessed in this retrospective audit. Therefore, it is not possible to estimate the relative impact of the study on total screening outcomes.

Background

All abnormal smear tests are referred to NHS Dumfries & Galloway colposcopy services. Therefore all participants of our studies are referred to colposcopy, if they have had an abnormal smear which meets the referral criteria. This gave us the opportunity to get some idea about the number of women who had had a smear test in the community without informing us. This was used as a surrogate marker of how effective our interventions were in terms of motivating defaulters to attend screening.

A small audit has revealed that the number of defaulters referred to colposcopy increased fourfold between early and mid- 2012. It was noted that the only defaulter with an abnormal

smear in March was seen in the third week of May at the colposcopy clinic. Similarly, most defaulters who came forward for screening may have been seen at colposcopy before 31 December 2012. Therefore, all new colposcopy referrals during (June- Dec 2012) and the comparable time in the previous year have been included in this audit.

Methods

A retrospective audit was carried out including colposcopy referrals made in Dumfries & Galloway in June to December 2012 and 2011. The primary aim of the audit was to find out the number of new defaulters referred to colposcopy in each year.

Hard copies of colposcopy clinic lists from March 2012 to January 2013 and from March 2011 to January 2012 were retrieved from two different sources: the appointments centre and Gynaecology secretaries. Both sets of clinic lists were cross-checked to ensure completeness. The screening history of each individual was checked in the SCCRS, in order to differentiate defaulters from regular screening attendees. The histological diagnoses of defaulters were checked in the Sci Store Live database. All findings were recorded on the clinic list as well as an Excel database. Care was taken to identify women who had been in the clinic list more than once due to various reasons. This audit was approved by the Clinical Governance Department.

Results

A total of 51 defaulters were referred to colposcopy from 1 June 2012 to 31 December 2012 out of 182 new SCCRS referrals. During the same period in 2011, 17 defaulters were referred to colposcopy out of 183 new SCCRS referrals (Table 4.5.1). A considerable proportion (51/182= 28%) of new colposcopy referrals were defaulters in 2012, in comparison to 2011 (17/183= 9%).

There were 28 CIN2+ (7xCIN2, 16xCIN3, 3xCGIN and 2xcacinoma) diagnosed in these 51 defaulters in 2012. There were 13 CIN2+ (8xCIN2, 5xCIN3, 0xCGIN and 0xcacinoma) diagnosed in these 17 defaulters in 2011. The number of new defaulters diagnosed with CIN2+ during June-December 2012 significantly increased in comparison to the same time period in 2011 (RR=2.2, 1.2-4.1). The number of CIN2+ was 15 less in the same period in 2011 (Fig 4.5.1).

Table 5.1.1: New colposcopy referrals in Dumfries & Galloway June-Dec 2012 & 2011

Year	2012				2011			
Month	clinics	new	def	cin2+	clinics	new	def	cin2+
June	7	22	3	1	6	20	3	2
July	10	42	15	10	10	36	3	3
Aug	5	21	3	2	4	20	2	2
Sep	7	22	6	4	8	32	4	3
Oct	8	26	11	5	8	23	1	1
Nov	7	22	6	2	8	26	1	0
Dec	8	27	7	4	6	26	3	2
Total	**52**	**182**	**51**	**28**	**50**	**183**	**17**	**13**

Key: clinics= number of colposcopy clinics per month; new= number of new colposcopy referrals per month; def= number of new defaulters referred to colposcopy per month; cin2+ histological diagnosis of high grade CIN or worse amongst defaulters.

Fig 5.1.1: Details of hg-CIN or worse (CIN2+) cases diagnosed amongst defaulters in each year

Histology	**2012**	**2011**
CIN2	7	8
CIN3	16	5
CGIN	3	0
Cancer	2	0

The number of new defaulters referred to colposcopy (Fig 4.5.2) during June-December 2012 significantly increased in comparison to the same time period in 2011 [OR=3.8 (2.1-6.9)].

Fig 5.1.2: Comparing number of new defaulters referred to colposcopy between June and Dec 2012 and the corresponding period in 2011.

```
. xi: logistic default i.year
i.year            _Iyear_2011-2012    (naturally coded; _Iyear_2011 omitted)

Logistic regression                               Number of obs   =        365
                                                  LR chi2(1)      =      21.92
                                                  Prob > chi2     =     0.0000
Log likelihood = -164.53663                       Pseudo R2       =     0.0625
```

default	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iyear_2012	3.801527	1.153618	4.40	0.000	2.097253	6.890729
_cons	.1024096	.0260788	-8.95	0.000	.06217	.1686945

Discussion

The number of new defaulters referred to colposcopy increased 3 folds (OR=3.8, 2.1-6.9) during the study period in comparison to the same period (June-Dec) in 2011.

The extra number of CIN2+ cases diagnosed in June-Dec 2012 was 15, in comparison to the same period in 2011. Assuming that all of these extra 15 cases were a consequence of the study, we attempted to estimate the number of defaulters diagnosed with CIN2+ after having been to a smear test (without HPV testing). We clearly know that two CIN3 diagnosed between June and December 2012 were participants who were first found to be HPV positive in vaginal samples. Therefore, up to 13 CIN2+ may have been diagnosed as a consequence of extra smear tests which were carried out in the community, because no abnormal smears (from women who ticked option-2) were referred to colposcopy from the hospital smear clinic. Prevalence of CIN2+ in women attending for cervical screening in England is about 1% (Health and Social Care Information Centre 2013). If the above assumption is correct, up to 1300 defaulters in Dumfries & Galloway might have had cervical smears in the community. This 1300 figure could be a little over-estimation, as the relative risk of CIN2+ in defaulters is higher than the general population.

There were 2 defaulters in May 2012. However, both of them had been to cytology just before 15 March, indicating that study participants were referred to colposcopy after May 2012. Whilst

most defaulters had been recruited before November, all recruitments were completed by mid-November.

The methodology of this audit limited its potential to measure the total screening outcome. Its focus was on the number of new defaulters referred colposcopy during the study period, in comparison to the same period in the previous year. Screening outcomes (diagnoses) of remaining new colposcopy referrals were not assessed. Therefore, it is not possible to estimate the relative impact of the study on total screening outcomes.

Conclusions

The number of new defaulters referred to colposcopy was significantly increased in during June-December 2012, in comparison to the same time period in 2011. Whilst the odds of diagnosing CIN2 or worse diagnosis in a defaulter was increased twice during the study, a marked increase in CIN3 or worse diagnosis was seen.

5.2 Cost analysis of offering multiple screening options to defaulters within 2 studies

Study question

What is the estimated cost of offering multiple screening options to defaulters in the 1000 and 200 defaulter studies?

Summary answer

If £2,200 extra money was spent offering multiple screening options to 1000 defaulters in two cycles, the total estimated number of defaulters screened over 6 months would be 230 (90 HPV tests + 140 smear tests) in the 'letter' method. If £4,300 extra money was spent offering multiple screening options to 1000 defaulters in two cycles, the total estimated number of defaulters screened over 6 months would be 300 (200 HPV tests + 100 smear tests) in the 'kit' method. The 'kit' method appears to be more cost effective than the 'letter' method in terms of the cost per self-sample collected and cost per one defaulter tested for HPV. In terms of total number of defaulters screened, the 'letter' method appears to be more cost effective.

What is known and what this body adds

About 60/1000 defaulters will go back to screening without any intervention over 6 months. If defaulters were offered multiple screening options which include self-sampling, this can be significantly increased. The relative cost-effectiveness between the 'kit' and 'letter' method is unknown. Based on the estimated screening uptake rates of the 1000 and 200 defaulter studies, the 'letter' method appears to be more cost effective than the 'letter' method in terms of the total number of defaulters screened. This evidence may be useful in developing self-sampling based screening models.

Limitations

All of our studies were not included in this analysis. Laboratory sample handling (human) costs were not included in this cost analysis, which should increase the amounts estimated to an extent. Estimated positive gains of screening outcomes (prevention of cancer morbidity and mortality) were not included in this analysis.

Background

The cost of testing using a smear test was £7.19 and the cost of HPV testing was £12.83 when the sentinel study was carried out in 2009, according to its report published in 2012. The cost of a HPV test kit and reagents (excluding laboratory handling costs) is currently about £9.00. However, a sample collection for a smear test can cost substantially more (Fig 5.2.1) than a sample collection for a self-collected vaginal HPV tests (Table 3.6.2). It appeared that supplying a self-sampling kit on-demand could be cost-effective as postage of a self-sampling kit was thought to be high.

Fig 5.2.1: Cost of sample collection for a smear test

cost of making an appointment
woman's time
travelling costs
clinician's time
chaperone's time
hand washing
hand towels
gloves
speculum
brushes
lubricant
gown for the woman (sometimes)
paper drapes to cover the couch
paper to cover for woman's privacy (sometimes a cloth)
absorbent (incontinent) pad
wipes
sanitary towel
disposal of this clinical waste
cost of running the clinic (estate costs)
cost of specimen transport
other costs

Methods

Costs of each step of screening were calculated. The number of women screened may be found from the study database. Calculations used in this analysis were based on methods and outcomes of the 1000 defaulter study which sent a multiple options letter to defaulters ('letter' method) and the 200 defaulter study which sent a self-sampling kit to defaulters ('kit' method).

Results

The cost of sample collection for a self-collected vaginal HPV test (2012) in the 'letter' method was £2.52. The 'kit' method costs less (£1.98) (Table 5.2.2). Of note, the franking price for 1000 Royal Mail First Class pre-paid envelops is £10 (10p each).

Table 5.2.1: Cost of one vaginal sample collection, 'letter' method

Item	£	p
Invitation letter (printing & sorting)		20
Postage		31
return postage		8
Kit letter (printing & sorting)		15
Rovers Evalyn brush kit	1	00
Jiffy bag		10
Kit sending letter envelope		5
Sending postage		53
Return first class pre-paid postage		10
Total	**2**	**52**

Table 5.2.2: Cost of one vaginal sample collection, 'kit' method

Item	£	p
Invitation & kit letter (printing & sorting)		20
Rovers Evalyn brush kit	1	00
Jiffy bag		10
Kit sending letter envelope		5
Sending postage		53
Return first class pre-paid postage		10
Total	**1**	**98**

The total extra cost (apart from the staff costs for HPV testing) of offering HPV screening to 1000 defaulters in a single cycle using the letter method would have been £1354, assuming 9% kit requests in a single cycle (Table 5.2.3). At the end of this, we predicted that about 60 women would have had HPV testing. The total cost (apart from the staff costs for HPV testing) of offering HPV screening to 1000 defaulters in a single cycle of the letter method would have been £1555, inclusive of the costs for 28 smear tests (28x7.19= £201.32) that HPV positives would have needed to have.

Estimating costs per 2 cycles is slightly more difficult as it depends on the total response rate of the first cycle, which varies. The total extra cost (apart from the staff costs for HPV testing) of offering HPV testing to 1000 defaulters in 2 cycles of the letter method would be £2220, assuming 15% total response (total number of defaulters choosing options 1 to 6), at the end of the first cycle. At the end of 2 rounds, about 130 women would request self-samplers, out of which 90 women would actually do it. The total cost (apart from the staff costs for HPV testing) of offering HPV testing to 1000 defaulters in 2 cycles of the letter method would be £2507, including the costs for 40 smear tests (287.60) that HPV positives would need to have.

Table 5.2.3: Cost differences between different self-sampling models

	Method	£	p	Number*	(£) Per head[$]
1	Collection of 1 vaginal sample, 'letter'	2	52	-	-
2	Collection of 1 vaginal sample, '**kit**'	1	98	-	-
3	Sample collection from 1000 in one cycle, 'letter'	772	16	62	12.45
4	Sample collection from 1000 in one cycle, '**kit**'	1980	00	175	11.31
5	Offering HPV screening to 1000 in one cycle, 'letter'	1354	10	62	21.84
6	Offering HPV screening to 1000 in one cycle, '**kit**'	3633	75	175	20.76
7	Offering HPV screening to 1000 in two cycles, 'letter'	2177	78	92	23.67
8	Offering HPV screening to 1000 in two cycles, '**kit**'	4275	50	200	21.38

*Note: These costs are based on methods and outcomes of our studies, conducted in 2012. *Number of self-samples returned. [$]Cost per sample collected/tested.*

Cost per one self-sample collected between the 'letter' model and the 'kit' model in a single cycle can be compared as follows: The total cost for the sample collection (£772) was lower in the 'letter' group in comparison to the 'kit' group (£1980). However, the proportion of self-samples received in one cycle (without a reminder) was less (6%) in the 'letter' model in comparison to the 'kit' model (17%). Hence, the cost per one sample collected in the 'letter' model (772/62= £12.45) was 10% more than that of the 'kit' model (1980/175= £11.31) [a total of 35 out of 200 kits which were sent in the first cycle in the 200 defaulter study have been returned]. Moreover, the total cost for sample collection in the kit model would be £1980, even if all 1000 defaulters or none of them decided to self-collect. This varied in the letter model.

Cost per one defaulter tested for HPV would be (1354/92=£21.84) in the 'letter' method, 1 cycle (Table 5.2.3). Cost per one defaulter tested for HPV would be (3633/200=£20.76) in the 'kit' method, 1 cycle.

Cost per one defaulter tested for HPV would be (2177/62=£23.67) in the 'letter' method, 2 cycles (Table 5.2.3). Cost per one defaulter tested for HPV would be (4275/200=£21.38) in the 'kit' method, 2 cycles.

Although there has been a marked rise in general postage seen between 2012 (£1980) and 2014 (£2030), the rise in franking prices is not very high. The stationery cost is unchanged. Therefore, the total cost difference is only £50.

Discussion

The number of new defaulters referred to colposcopy during the study period (June-December 2012) was significantly higher than the same period in 2011. Although 8-9% women informed us that they wished to get a smear test, the actual number that had smears could have been higher. Although it is not possible to find the number of defaulters who had smears without informing us in the 1000 and 200 and 2000 defaulter studies, it was possible in the 'Older' and 'Younger' defaulter studies (Table 4.7.3). Although 28 out of 584 defaulters informed us that they wished to have a smear test at 6 months by ticking the option-1 and option-2, 47 had smears in the 'Older' defaulter study. Although 133 out of 1441 defaulters informed us that they wished to have a smear test at 6 months, 218 had smears in the 'Younger' defaulter study. This indicates that if 161 defaulters inform us that they wish to have a smear, 265 will actually have it (x1.65).

This is almost the opposite trend of self-sampling, where 284/383 (74%) actually returned a sample. A total of 86 women in the 1000 defaulter study wished to have a smear test. It could be estimated that 142 (86x1.65) might have had smears at 6 months. A total of 13 women in the 200 defaulter study wished to have a smear test. It could be estimated that 21 (13x1.65) might have had smears at 6 months.

A total of 92 (9%) in the 1000 defaulter study, 40 (20%) in the 200 women study did HPV self-testing.

Summary

Cost per one self-collected sample returned for HPV screening in the 'kit' method is £1.14 cheaper than the 'letter' method (Table 5.2.3). Two cycles of 'kit' method is 1.2 times more expensive than a single cycle, which increased the self-sampling uptake by 1.1 times. Two cycles of 'kit' method is 1.6 times more expensive than a single cycle, which increased the self-sampling uptake by 1.5 times. Therefore, a second cycle (reminder) appears to be equally cost-effective in collecting self-samples in the 'kit' as well as in the 'letter' method.

The 'kit' method (£11.31) appears to be more cost effective than the 'letter' method (£12.45) per one self-collected sample returned. The 'kit' method (£20.76) appears to be more cost effective than the 'letter' method (£21.84) per one defaulter tested for HPV in a single cycle. A similar trend is seen in the 'two cycles' model (Table 5.2.3).

If £2,178-£4,276 extra money is spent offering multiple screening options to 1000 defaulters in two cycles, 90-200 of them may have HPV testing. It can be predicted that additional 100-140 of them might have smears. This means that total estimated percentage of defaulters screened would be 23% (£9.47 per defaulter screened) in the 'letter' method and 30% (£14.25 per defaulter screened) in the 'kit' method. If £1,354-£3,634 extra money is spent offering multiple screening options to 1000 defaulters in one cycle, 62-175 of them may have HPV screening. It can be predicted that additional 75-100 of them might have smears. This means that total estimated percentage of defaulters screened would be 16% (£8.46 per defaulter screened) in the 'letter' method and 25% (£14.54 per defaulter screened) in the 'kit' method. In terms of total number of defaulters screened, the 'letter' method appears to be more cost effective.

Conclusion

If £2.2-4.3*k* extra was spent offering multiple screening options to 1000 defaulters in two cycles, 230-300 of them could be brought back to screening over 6 months. If £1.4-3.6*k* extra was spent offering multiple screening options to 1000 defaulters in one cycle, 160-250 defaulters could be brought back to screening. This will significantly increase the number of new defaulters referred to colposcopy.

The 'kit' method (£11.31) appears to be more cost effective than the 'letter' method (£12.45) per one self-collected sample returned. In terms of total number of defaulters screened, the 'letter' method appears to be more cost effective.

CHAPTER 6

Surveys

Introduction to chapter 6

The chapter 6 includes surveys conducted as a part of this study. There were two main methods of data collection- 3 questionnaires, free text boxes of option lists and the content analysis of the consultation when defaulters presented at the hospital smear clinic.

6.1 Acceptability of Evalyn brush as a self-sampling device.

Study question

How acceptable is the Evalyn brush for vaginal self-sampling to cervical screening programme defaulters?

Summary answer

The Evalyn device was fairly well accepted (217/311=70%) by those who requested self-sampling. Self-sampling experience was highly rated (86-97%) by 272 women who self-collected.

What is known and what this body adds

Almost all (98%) participants who were 134 patients visiting the gynaecology outpatient clinic in The Netherlands rated their Evalyn brush experience as good or excellent. Its acceptability in other settings, especially by non-attendees, is unknown. It appears that Evalyn brush was fairly well accepted by defaulters who decided to self-collect. It was highly rated by those who have self-collected, which encourage its use in non-attendees.

Limitations

The questionnaire had only ‘yes’ and ‘no’ answers. It did not have a ‘don’t know’ or ‘unsure’ column which may have changed the shape of the survey outcome. Our study was not designed to compare the acceptability between different samplers that the relative acceptability of Evalyn brush is unknown. Evalyn brushes were provided free of charge by the Rovers medical devices. However, the company did not play any role in this study apart from being a valued sponsor.

Background

According to the manufacturer, the Evalyn brush has been well accepted for self-sampling in a limited number of women in The Netherlands. There was no published evidence on its feasibility when we started our study. Our aim was to see if the device was acceptable to a sample of British women. We wanted to collect both objective and subjective evidence about this self-sampling kit.

Methods

We designed a simple questionnaire (Questionnaire 1 Fig 8.2.7, Appendix 2,) which was sent with the Evalyn brush to women who wished to self-collect. We advised them to fill the feasibility questionnaire after self-collecting a sample and return it with the sample in the pre-paid envelope.

The last objective question of this feasibility questionnaire was “If you had the option of self-sampling, is it more likely that you would regularly participate in future cervical screening?” This question was repeated in Questionnaire 2 (Fig 8.2.8, Appendix 2), which was administered when HPV positives came to the hospital smear clinic for a cervical cytology (smear) test, approximately 2 months after they had self-collected the sample.

Results

A total of 284 Evalyn samples were returned. All except 8 women returned the completed questionnaire along with the sample. All of these 8 women subsequently retuned the questionnaire with the consent form, after a reminder letter. No one returned the questionnaire alone (without a sample). Four questionnaires were lost (could not be found for analysis). The remaining 272 questionnaires were analysed.

The analysis of these 272 questionnaires is as follows (Table 6.1.1). Almost all (264/272=97%) said that the information provided was clear enough to self-collect a sample. They did not wish any additional information (97%). They found that self-sampling was easy (97%) and acceptable (96%). Whilst 11% found that self-sampling was uncomfortable, it was painful for 4%.

Table 6.1.1**:** Results of 272 feasibility questionnaire (Questionnaire 1) analysis

	Yes	%	No	%	No answer	%
Was the information **clear** enough to self-collect a sample?	264	97	4	1	4	1
Did you wish **more information**?	2	1	265	97	5	2
Was self-sampling **easy**?	265	97	4	1	3	1
Was self-sampling **uncomfortable**?	30	11	235	86	7	3
Was self-sampling **painful**?	12	4	256	94	4	1
Is self-sampling **acceptable** to you?	261	96	8	3	3	1
If you had the option of self-sampling, is it more likely that you would regularly participate in future cervical screening?	265	97	4	1	3	1
Please add any comments you may have below						

A total of 265 (97%) women said (at the time of self-sampling) that if they had the option of self-sampling, they would regularly participate in future cervical screening. A similar intention was noted when HPV positives came to the smear clinic where 99/105 (94%) answered ‘yes’ to the above question (Fig 6.1.1).

Fig 6.1.1: Results of 105 Questionnaire-2 analyses (answer to the second last question)

Question	Yes	No	No answer
If you had the option of self-sampling, is it more likely that you would regularly participate in future cervical screening?	99 (94%)	4 (4%)	2 (2%)

Subjective comments made in the free text box of the Questionnire-1 were analysed separately (Fig 8.1.6, Appendix 1). Comments were categorised into ‘practical reasons’, ‘attitudinal reasons’, ‘screening is not indicated’ or ‘the information is not clear’ to put into one of above 4 categories. For descriptive purposes, some (26/68) of comments written by defaulters are categorically presented in the Fig 6.1.2.

Fig 6.1.2: Free comments made in questionnaire-1

(a) practical reasons

- "I suffer from IBS so I don't like to have people prodding at me at times when it flares up."
- "I suffer from agoraphobia so it makes it difficult to get to surgery"
- "I suffer from a very unpleasant vaginal discharge, too embarrassed to allow a doctor to perform a smear"
- "I have some memory problems" (56 years)
- "I have very painful hips & this form of screening was much more comfortable"
- "I personally know my GP and the practise nurse I have had a bad smear experience at my practice"
- "I have been sexually abused"
- "Self sampling may be the only way transgender persons will have screening"
- "Fibroids obstructing the cervix - taking a smear was unsuccessful in 4 different days"
- "I find it extremely painful to have a normal smear test and this was painless, easy & quick." (43 years, last smear 2008)
- "Previously the nurse had a problem due to the position of the cervix- is this sample adequate?" (HPV positive, 48 years, 2006)
- "This way of screening is much more private and so much easier to fit into your life " (41 years, last smear 2008)
- "Nice to be able to do it at home when you are free and relaxed. Thank you." (44 years, last smear 2001)

(b) attitudinal reasons

- "I have made it to 32 years old without having a smear- ridiculously avoided because of embarrassment. If this self sampling was an option, I would participate and get tested regularly." (32 years, never had a smear)

(c) screening was not indicated

- "Declined last smear invite as I work in NHS England ad for me invite would be given not 3 years as NHS Scotland".
- "This was easy to do, as I never had one before as I am not sexually active and I have not had sex yet".

(d) the reason is not clear

- "I would do this every year rather than go to doctor, even though my doc is great!" (36 years, last smear 2000)
- "No lasting after effects, but didn't expect spotting." (54 years, last smear 2007)
- "Slightly uncomfortable, noted small spot of blood after taking sample." (56 years, last smear 2006)
- "I was sore on insertion but the test was easy and once inside was OK" (57 years, last smear 2008)
- "I don't think I should have to take part in a study to have this option." (56 years, last smear 2003)
- "So much paper to work through may put people off participating in this study." (55 years, last smear 2006)
- "Needed translation" (Eastern European, never had a smear)
- "I did struggle with trying to work out how to seal the bag!" (46 years, last 2005)
- "It would have been better (for the kit) to come in a Jiffy bag." (60 yr, last 2003)
- "No mention about the absorbent paper in the instruction leaflet." (this has been removed by the participant, 55 years, last smear 2006)

Free comments were written by 25% (68/272) defaulters who completed the Questionnaire-1. Whilst 11/ 37 (30%) defaulters over the age of 55 wrote some comments, younger defaulters did so less often (57/235=24%). The reason was not clear in 59% (40/68) statements (Fig 6.1.2). According to written information, screening did not appear to be indicated for 3% who made free comments. When the reason for defaulting is clearly stated, it appeared to be a practical reason

for a majority (23/26=88%) of respondents and attitudinal reason for 12%. General attitude of the comments appeared positive in 60%, negative 22% and not very clear in 18% (Fig 6.1.3).

Fig 6.1.2: Reason for not going for smears

	Category	N	**%**
a	Practical	23	**34**
b	Attitudinal	3	**4**
c	Not indicated	2	**3**
d	Not clear	40	**59**
	Total	68	**100**

Fig 6.1.3: General attitude of the comment made

	Category	N	**%**
1	Positive	41	**60**
2	Negative	15	**22**
3	Not clear	12	**18**
	Total	68	**100**

Discussion

The majority (70%) of women who requested the kit have returned a sample. It was well accepted for those who had done the test. Most women who self-sampled may have hoped that they would be tested negative, as they had to come for a smear test if they were tested positive. Therefore, our aim was to check if they still accepted this even if they had to come for a smear test in consequence. We administered Questionnaire-2 whilst the HPV positives were waiting for the smear test at the hospital smear clinic. Still, almost all of them said that they would regularly participate in future cervical screening, if they had the option of self sampling. This was a surprise answer for us.

A recently published study (Darlin, Borgfeldt et al. 2013) collected data in a way that is similar to ours by sending a questionnaire for those who failed to respond 1 month since the first contact. This detailed questionnaire covered their reasons for not attending the organized cervical screening programme, their sexual history, parity, smoking habits and educational level. The

most common reason given for nonattendance by non-attendees was “Uncomfortable with vaginal examination” (37%) followed by previous negative experiences of gynaecological examinations (25%). The same trend was seen in the smear group. Other common reasons were “Feel healthy”, “Lack of time” and “Experience of unfriendly health workers” indicating that a vast majority were practical reasons for non-attendance. These Swedish findings are comparable to ours.

Conclusions

The Evalyn device was fairly well accepted (70%) by those who requested self-sampling. It was highly rated and commended by women who have actually self collected a sample and returned it. Furthermore, 97% of them said that they would regularly participate in future cervical screening, if they had the option of self-sampling, soon after the self-collection. A similar intention was noted when HPV positives came to the smear clinic about 2-3 months after the self-collection. When the reason for defaulting was clearly written by those who self-collected, it appears to be a practical reason for a vast majority (88%).

6.2 What are the barriers to cervical screening? Results of 2 surveys

Study question

What are the barriers to cervical screening?

Summary answer

Practical barriers to cervical screening appear to have more effect than attitudinal barriers to the HPV positive defaulters who came to the hospital smear clinic.

What is known and what this study adds

Practical barriers to cervical screening appear to have more effect than attitudinal barriers in the UK. The survey of 105 HPV positive defaulters who came to the hospital smear clinic supported the above evidence. According to the free comments provided by 20% of women who returned an option list, screening was not indicated for 86% (98/114) defaulters who opted-out (but still returned a questionnaire), compared with 19% (12/62) of those who opted-in. Precise reasons why most of defaulters were screened may never be undestood (due to lack of engagement). However, reasons that we explored may be representative of them.

Limitations

Opinion of defaulters who opted in for self-sampling could be biased. Only 695 (20%) defaulters responded to the initial invitation letter so the opinion of the majority is unknown.

Background

The coverage of smear tests within the recommended screening interval (usually 3 or 5 years) was above 80% in only three European countries in 2004 (Anttila, Ronco et al. 2004)

Factors that negatively affect cervical screening uptake has been categorised into 3 by Waller (Waller, Bartoszek et al. 2009).

a) demographic factors such as age, marital status and ethnic group
b) structural/ health-care factors such as appointment times, female practitioners and 'friendly treatment'
c) attitudinal factors like embarrassment trust and concerns about discomfort.

However, when both women who attended and did not attend for screening were interviewed (Waller, Bartoszek et al. 2009), practical barriers to cervical screening seem to have affected more than the negative attitudes for non-attendance. Pain (68%) and embarrassment (79%) were the two main issues associated with smears for working women in China who had ever attended screening (Holroyd, Twinn et al. 2001).

The aim was to describe and interpret why women with no cervical smear taken during the previous recommended interval chose not to attend the national cervical screening programme.

Methods

Data was collected using two sources: Questionnaire 2 and the free text comments made in the options list.

Vaginal HPV positives of our main study came for a hospital smear test. The clinic receptionist requested the participant to fill in Questionnaire 2 when they handed in the appointment letter. Women filled the questionnaire whilst they were waiting for their smear test and put them in the questionnaire box sitting on the waiting area desk.

All defaulters aged between 30 and 55 were sent a multiple options list along with each screening letter (both initial invitation as well as the reminder). Many wrote free text comments when they returned the option list (requesting a kit, requesting a hospital smear clinic appointment etc.). In very small number of cases, defaulters or someone else on behalf of the defaulter contacted us, usually by telephone explaining their circumstances. Such comments were prospectively recorded by the Data Manager of the Research & Development Department. These subjective comments are presented in (Fig 8.1.7, Appendix 1).

These free text comments were categorised into one of the following 4: ‘practical’, ‘attitudinal’, ‘not indicated’ and ‘not clear’. If the comment written did not clearly explain the reason why the defaulter had not had screening, it was categorised as “not clear” (NC). When screening was not indicated for a clearly defined reason or on other reasonable grounds, it was categorised as “not indicated” (NI). When the reason for non-attendance was more likely to be an attitudinal it was categorised as “attitudinal” and practical as “practical”. These were individually categorised by the PI and Dr Gwen Baxter (co-investigator). Any disagreements were discussed to come to a consensus.

Results

1. **Analysis of Questionnaire 2**

A total of 105 Questionnaire-2 were analysed (Table 6.2.1a - Table 6.2.1c).

Table 6.2.1a: Results of Questionnaire-2 analysis, the number of defaulters endorsed 'yes' to each question

No	Statement	Yes	No	No answer
1	Smear tests are embarrassing	72	31	2
2	I intend to go when I am due, but I don't always get round to it straight away	73	29	4
3	I worry that a smear test will be painful	45	58	2
4	I'm scared of what a smear test might find	61	39	5
5	I've had a bad experience of a smear test in the past	31	72	2
6	It is difficult to get an appointment to fit in with work/childcare commitment	41	62	2
7	I don't feel at risk of cervical cancer	26	71	8
8	I'm not sexually active so I don't need to go for a smear test	9	90	6
9	I do not trust the smear test	16	85	4
10	I do not need a test if I do not have any symptoms	12	88	5
12	If you had the option of self sampling, is it more likely that you would regularly participate in future cervical screening?	99	4	2
13	I have never had a smear test	9	85	56
14	My last smear was …. years ago (number of times a figure is written)	75	n/a	30
15	**Please write any other reason/comments you may have, below (number of comments written)**	14	n/a	91

Table 6.2.1b: Results of Questionnaire-2 analysis- attitudinal barriers

No	Statement	Yes	No	No answer
1	Smear tests are embarrassing	72	31	2
3	I worry that a smear test will be painful	45	58	2
4	I'm scared of what a smear test might find	61	39	5
7	I don't feel at risk of cervical cancer	26	71	8
8	I'm not sexually active so I don't need to go for a smear test	9	90	6
9	I do not trust the smear test	16	85	4
10	I do not need a test if I do not have any symptoms	12	88	5

Table 6.2.1c: Results Questionnaire-2 analysis- practical barriers

No	Statement	Yes	No	No answer
2	I intend to go when I am due, but I don't always get round to it straight away	73	29	4
5	I've had a bad experience of a smear test in the past	31	72	2
6	It is difficult to get an appointment to fit in with work/childcare commitment	41	62	2

Questions were sorted into two categories: attitudinal barriers (statement numbers 1, 3, 4, 7, 8, 9 & 10) or practical barriers (2, 5 & 6). The number of women answered 'yes' to each question was analysed. Practical barriers to cervical screening affected more than attitudinal barriers (RR=1.4, 1.20-1.64).

2. Analysis of free comments made in the screening option lists

Many (183/695=26%) defaulters wrote free text comments when they returned option lists. They were categorized into 4 categories: practical, attitudinal, not indicated and not clear. Analysis of these 4 categories is presented in the Table 6.2.2. Five (3%) women who didn't choose any option were removed from analysis.

Table 6.2.2: Analysis of free comments made by respondents

Category	**1** GP smear	**2** Hospital smear	**3** HPV hospital	**4** HPV home	**5** Discuss	**6** Opt out	**Total**
Practical	6	6	0	7	2	7	28
	21.43	50.00	0.00	36.84	100.00	6.14	15.73
Attitude	2	0	1	7	0	3	13
	7.14	0.00	33.33	36.84	0.00	2.63	7.30
NI	11	1	0	0	0	98	110
	39.29	8.33	0.00	0.00	0.00	85.96	61.80
NC	9	5	2	5	0	6	27
	32.14	41.67	66.67	26.32	0.00	5.26	15.19
Total	28	12	3	19	2	114	178
	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Abbreviations: NI= not indicated; NC not clear

Whilst defaulters who opted-out chose the option 6, those who opted-in chose options 1 to 4. Screening was not indicated for 98 out of 114 those opted-out (86%) than those who opted-in (12/62=19%). This difference was significantly different OR=25.5 (11.2-58.1). However, only 20% (695/3498) of defaulters returned the options list (624 defaulters selected options 1-5 and 71 selected option number 6). A total of 2803 (80%) defaulters did not respond. These 2803 non-responders' opinion is unknown which could totally change this result.

Discussion

It could be argued that if question number 5: "I've had a bad experience of a smear test in the past" belongs to 'practical barriers'. A bad experience when getting a smear test can be caused by various factors. It could depend on a woman's menopausal status, menstrual status, pelvic anatomy, sensory (pain) syndromes and attitude, as well as healthcare factors, such as available resources (e.g. an adjustable examination couch that is designed for this purpose,

appropriate lighting, and different types of specula), together with the skill, behaviour and attitude of the smear taker. This may not recur. The woman's attitude is only one of many factors. A woman with a normal attitude towards screening could also experience a bad smear test. Therefore, it is categorised under practical reasons. However, "I am worried that my previous bad smear experience could occur again" is better categorised as an attitudinal barrier.

It could be argued that embarrassment is a neutral attitude rather than a negative attitude. It is possible that embarrassment would be similarly endorsed by regular attendees and defaulters. The questionnaire survey was anonymous. Women attending at the hospital smear clinic could pick a questionnaire from the clip board. They knew that it will be put into a big box which was kept on the middle desk of the clinic waiting area. The questionnaire did not have any reference number or space to write down a name. Hopefully, this gave them some reassurance that the information that they put down would be anonymous. This was clearly stated in the questionnaire too.

Conclusions

Practical barriers to cervical screening had more effect than attitudinal barriers to 105 HPV positive defaulters who came for a hospital smear test. One in five (n=695) of the target population returned the options list. Screening was not indicated in 98 out of 114 defaulters who opted-out (86%) than those who opted-in (12/62=19%).

6.3 What is acceptable for defaulters who refused our multiple screening options?

Study question

What form of screening would be acceptable for defaulters who refused our multiple screening options?

Summary answer

The response rate to this survey is 1-2% (38/2419). All 38 respondents stated that if they could be screened using a sample of urine, they will accept that offer. Half of them made some suggestions about how the testing could be made more acceptable to them. They appeared to have a positive attitude toward screening and suggestions were generally constructive.

What is known and what this body adds

Although much research has explored reasons why women did not attend routine screening, no study has been conducted to see what is appropriate for women who declined the offer of multiple screening options which included self-sampling. The response rate to this survey was very low, indicating that the answer is still unknown. Questionnaire surveys do not appear to be an effective method in exploring this research question.

Limitations

The poor response rate 1-2% is the main limitation of this survey. However, overcoming this limitation may not be easy in accessing this hard-to-reach group of people.

Background

Despite our best efforts, the majority of defaulters in Dumfries and Galloway still remain unscreened. The aim of questionnaire 3 was to explore this. The maximum screening uptake of any community based self sampling study was 39%. Further improvement of the screening uptake may have been achieved by answering the question: what can make them accept a cervical screening test?

Methods

All defaulters aged between 30 and 55 who did not respond to the initial invitation (n=2714) were sent Questionnaire 3 and a reminder, 3 months (2 months in the 2000 women study) after the first invitation letter. There were 2 text boxes in view to collect qualitative data and only one objective question in this simple questionnaire (Fig 6.3.1). Questionnaires retuned intact, for example, a woman retuning an empty Questionnaire 3 with the option list ticked in any given box, was not included in the analysis.

Fig 6.3.1: Questionnaire-3

Reasons why I declined the testing.

.....

.....

.....

Suggestions about how the testing could be made more acceptable for me.

.....

.....

.....

If you could be tested using a sample of urine would you accept that offer?

Please answer yes or no

YES ☐ NO ☐

Thank you for completing this questionnaire.

Results

Although 2714 questionnaires were sent, it was not relevant to women who had been to a smear test without informing us, which are about 295 according to the sensitivity analysis.

A total of 45 (1.7%) questionnaires were returned, of which 7 were returned blank with a completed options list. It could be assumed that these 7 questionnaires may not have been returned, unless the option list was returned. Remaining 38 questionnaires were filled, at least partially.

All those who attempted to fill the questionnaire (38/38=100%) answered yes, to the urine sample question.
Subjective comments were written in 31 questionnaires. Reasons for not having any screening test so far are listed in Fig 8.1.9 in the Appendix 1. These reasons were categorised into 4 different categories: 'practical', 'attitudinal', 'screening is not indicated' or 'not clear'. Their suggestions to make screening acceptable to them are listed in Fig 8.1.10 in the Appendix 1. It was categorised whether their suggestions were positive or not.

A total of 31 (86%) women wrote something in free text boxes. Screening was not indicated for 5 (16%) out of 31 of them. Whilst 15 (48%) were practical reasons 11(35%) were attitudinal reasons (Fig 6.2.1).

Half of them (19/38= 50%) made some suggestions about how the testing could be made more acceptable to them. All of them appeared to have a positive attitude toward screening and suggestions were generally constructive.

Fig 6.3.2: The main categories of reasons for not accepting screening

Category	**n**	**%**
Practical	15	39
Attitudinal	11	29
Not indicated	5	13
Not relevant	0	0
Not stated	7	18
Total	38	99

Discussion

The response rate is very low [38 ÷ ((total list=3498) – (list clearance=267) – (responded to the initial letter=517) – women who had smears without informing us))]. According to the sensitivity analysis, it is estimated that about 295 women might have had smears without informing us. Therefore, the response rate is calculated to be 38/2419=1.6%.

According to the findings of the 1996-97 Canadian National Population Health Survey which included 33,817 women (Maxwell, Bancej et al. 2001), for those who hadn't had a smear test

during the last screening interval; most (53%) reported that they did not think it was necessary. This fact may be applicable to our cohort of defaulters who did not accept any method of screening, despite having multiple options. Screening was not indicated for a vast majority of those who opted out by choosing option 6 of our intervention.

Conclusion

The response rate to this survey was very low (1-2%), indicating that a questionnaire survey is an ineffective research tool to explore this question. All 38 respondents answered 'yes' to the question 'if you could be tested using a sample of urine would you accept that offer?' Half of them (19/38= 50%) made some suggestions about how the testing could be made more acceptable to them. All of them appeared to have a positive attitude toward screening and suggestions were generally constructive.

6.4 What was the main barrier to cervical screening? A content analysis of the smear clinic consultation

Study question

What was the main barrier to cervical screening for women who defaulted?

Summary answer

According to the content analysis of the smear clinic consultation, practical barriers to cervical screening appear to have more effect than negative attitudes for non-attendance to this cohort of 155 defaulters.

What is known and what this study adds

Practical barriers to cervical screening appear to have more effect than attitudinal barriers in the UK. This qualitative study conducted amongst 155 defaulters strengthens the current evidence.

Limitations

Opinion of defaulters who opted in for screening could be biased. Interview with the defaulter was not tape recorded which limits the reproducibility of the data. Most of these HPV positive defaulters took part in more than one survey.

Background

It has been highlighted that non-attendance is due more to the practical barriers than attitudinal barriers. Reasons may vary in different geographical locations.

Methods

A content analysis of the smear clinic consultation where either under or unscreened women were seen. HPV positives of our main study came for a hospital smear test. Each woman was properly counselled by the PI before the smear test was taken. At the end of counselling, each participant was asked one clear question: what was the main reason why you didn't go to your last smear test? We waited for the woman's reply, for as long as it took. However, most women gave a quick answer. A few of them gave various reasons, of which the first answer was recorded on the data sheet. Care was taken not to facilitate their answer. The PI decided whether it was a practical or attitudinal reason there and then and recorded it next to the reason.

Some came to a hospital smear clinic without having a HPV test. For those who had previously provided a self-sample, the result (HPV negative or positive) was known by the time they attended the hospital smear clinic.

Results

Prospectively collected data are presented in Fig 8.1.8 in Appendix 1. The main reason for non-attendance is categorised into 4- 'practical', 'attitudinal', 'screening not indicated' and 'not clear'.

A total of 142 out of 155 reasons were recorded. They were categorised into 4. The main reasons for 'not clear' were 'no spontaneous answer' and 'forgot to record'. Please find the analysis of data in Fig 6.4.1. These cohort of defaulters faced practical barriers to cervical screening more than negative attitudinal barriers [RR=4.9 (3.3-8.0)]. Practical barriers to cervical screening appear to be similarly affecting both defaulters who opted for self-sampling and had a positive test as well as for those who did not wish to self-collect (Fig 6.4.2).

Fig 6.4.1: The main categories of reasons for not going for the previous smear

Category	**n**	**%**
Practical	113	73
Attitudinal	22	14
Not indicated	7	5
Not recorded	13	8
Total	155	100

Fig 6.4.2: Analysis of the main reason for not going for the previous smear between HPV positive defaulters versus defulters who did not wish to self-collect

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. tab hpv category, chi2
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	Category				
HPV	Atti	NC	NI	Pract	Total
N	3	6	4	39	52
Y	19	7	3	74	103
Total	22	13	7	113	155

```
          Pearson chi2(3) =   6.6345   Pr = 0.085
```

The main reason for non-attendance could be grouped as follows (Fig 6.4.3):

Fig 6.4.3: The main reasons for non-attendance

(a) Practical

1. Busy at work or with the family or both
2. A regular attendee experiencing a bad smear test
3. Illnesses such as dementia, IBS, arthritis, bipolar disorder and genital atrophy
4. Personal problems
5. I want to avoid my practice' smear taker
6. Received appointment letter, but didn't get round to it
7. Received an appointment letter, but I was pregnant then
8. Didn't receive a letter
9. Change of address
10. Lack of understanding
11. Lack of communication or poor care by the healthcare staff

(b) Attitudinal

1. Embarrassment
2. Anxiety and phobia
3. Didn't want to know

Many defaulters thought that screening was not necessary as they were either not sexually active at that time or had not been sexually active for a long time (for example, widows and women who were not in a relationship). Only a few women said it was for no apparent reason.

Discussion

Some defaulters believed that they didn't have to go for screening, if they were not at risk of getting a sexually transmitted infection (STI). Consequently, they took screening less seriously either since they had been in a stable, monogamous relationship for a long time or since they had ceased sexual activity completely. This was not an attitudinal reason. It was mainly lack of understanding for which the National Screening Programme and healthcare professionals should have taken some of the responsibility. I am yet to find a patient information leaflet that clearly states that the HPV infection has the potential to stay in the genital tract forever

(although 90% women who are exposed to HPV are likely to clear the infection within a few years). Perhaps, this knowledge gap should be closed by educating the public. The defaulter reminder letter and the screening information leaflet should be amended appropriately.

A few factors may have biased this information:

1. The background of these women who came for a smear test. Whilst most came after being tested positive for HPV, others came for a smear test because they did not want to go to the place that they usually go or were supposed to go. Hence, there was a natural tendency that they would praise us or our study. In order to reduce this bias, we asked this question at the very beginning of the consultation, soon after a rapport had been built. We tried to create a neutral environment and adopt a neutral behaviour. We did not patronise anyone's (community smear takers) behaviour nor did we incriminate it whilst collecting this information.
2. The professional role of the PI (Gynaecologist in the NHS) and the gender (male). However, most women seemed to be genuine about their opinion. The PI was always accompanied by a senior healthcare assistant.
3. The defaulter's state of mind; i.e. some were self-blaming, some were blaming the setup, some were slightly concerned, some were neglecting and a few were seriously worried, some or all of which may have attributed to it.

It could be argued that embarrassment is a neutral attitude rather than a negative attitude.

"How do women who choose not to participate in an organised screening programme reason about their decision?" was the research question of a qualitative research conducted in Sweden (Blomberg, Ternestedt et al. 2008). Women contacting the central organization, who neither wished to participate in the organised cervical screening programme at that time nor in the future, were the subjects of the study. Qualitative telephone interviews and fax messages from women who actively declined participation were analyzed inductively. Factors related to the women's decisions not to participate in screening at all include:

1. lack of confidence in the benefits of screening
2. previous negative health care and preventive experiences
3. a belief in the individual's own ability to discern health changes
4. a belief that the individual was not at risk for cervical cancer
5. a number of unconventional standpoints on social and political issues

Our study findings were somewhat similar to these findings, although the method of sampling varied significantly. A cohort of women who contact the central organization expressing their unwillingness to participate was quite different from that of the woman who wished to do it in a different way. However, the research question is almost the same: 'what was the main reason why you haven't been to your last smear test?' Keeping with the difference in women being interviewed, the Swedish cohort appears to have had more attitudinal barriers than our cohort. This can be interpreted as women who wished to accept alternative screening being more likely to have practical barriers to cervical screening than women who totally declined screening.

A qualitative study examined the barriers to cervical screening in an urban setting in Canada (Fitch, Greenberg et al. 1998). Focus group methodology was used to explore the perspectives of socioeconomically disadvantaged women regarding their access to health care. The study revealed four broad themes:

1. being able to talk with doctors is important
2. being treated as a person is important
3. finding answers to many questions about cancer is important
4. having a Pap test is uncomfortable

Data collected from nine focus group discussions with 62 women from diverse socio-economic backgrounds in Serbia (Markovic, Kesic et al. 2005) identified that the interplay of social and personal barriers influenced poor screening attendance. A series of focus groups among African Caribbean, African, Gujarati, Pakistani, Greek and Arabic groups living in Brent and Harrow in the UK, which consisted of 85 women and 50 men were conducted to discover their perceptions of cancer screening and the barriers to effective uptake (Thomas, Saleem et al. 2005). Analysis of focus group data revealed that interplay of practical and attitudinal factors affected screening participation. It was revealed that poor knowledge, underlying health and cultural beliefs, attitudes, language and unhelpful attitudes of health professionals were all important barriers.

Women who reported that their last test had been painful (bad experience) or embarrassing held more negative views of a future test (Orbell 1996). These were the reasons for non-attendance for many women in our cohort. The ways in which cervical screening discourses were negotiated, accepted and resisted by British women appears complex (Bush 2000).

Conclusions

Practical barriers to cervical screening appear to have more effect than negative attitudes for non-attendance [RR=4.9 (3.3-8.0)] to this cohort of defaulters. Defaulters who opted for self-sampling (and had a positive test) as well as those who opted for a smear test alone (without doing self-sampling) were similarly affected by practical barriers.

6.5 Patient experience survey at the hospital smear clinic

Study question

What was the overall experience of women attending at the hospital smear clinic when screening programme defaulters were offered multiple smear options?

Summary answer

The hospital 'out of normal working hours' smear clinic was highly rated by patients.

What is known and what this body adds

Hospital smear clinics are no longer available within the NHS. Hence, its acceptability and necessity is unknown. This survey shows that the hospital smear clinic was acceptable to those defaulters who attended. The hospital 'out of normal working hours' smear clinic was highly rated by its service users. All 3 smear clinics were equally rated. No serious adverse comments were made by clinic attendees. Running a hospital smear clinic at a frequency which is governed by its demand (e.g. first Wednesday and/or first Saturday of the month) may be recommended. This may widen women's choice.

Limitations

User surveys can be biased due to various reasons. Although we attempted to minimise such, there was room for bias.

Background

Previous bad smear test experience was one of the main practical reasons for non-attendance for under-screened women. The aim was to evaluate the patient experience of women attending the hospital smear clinic by administering a simple questionnaire in view of exploring the things that we do better and not as well. These findings could be used for service development.

Methods

All patients attending at the hospital smear clinics from October to November 2012 were requested to complete a simple patient experience survey questionnaire as they left the smear clinic. This was requested by the nurse or healthcare assistant on the smear clinic. Patients

filled it in outside the smear clinic and put in the 'Patient Feedback' box in the waiting area. Women didn't know about the questionnaire until they left the clinic. The nurse was supposed to say "Can you please fill this questionnaire about this clinic and put it in this box?" Care was taken not to influence patient's decision making.

Separately coloured questionnaires (Fig 6.5.1) were administered for lunch time (green), evening (yellow) and weekend (pink) clinics.

Fig 6.5.1: User survey questionnaire of the hospital smear clinic

Smear Clinic (please tick)	Yes	No	Unsure
Did we meet your expectations?			
If this service was available in the future, would you use it again?			

How would you rate this service?					
1 = poor, 5 = excellent (please circle)	1	2	3	4	5
Any suggestions for improvement					

Thank you for your feedback.

Results

Feedback of smear clinics is illustrated in Fig 6.5.2.a to Fig 6.5.2.f. Fifty five women attended the hospital smear clinic during the survey period. A total of 55 slips were found in the box. All of them were filled. Almost all 54 (98%) said that their expectations were met. A similar proportion (53/55=96 %) said that if this service was available in the future, they would use it again. The overall rating of the smear clinic experience was very positive with no one rated 1 or 2. Three (5%) rated 3, 9 (16%) rated 4 and 43 (78%) rated 5. Some suggestions for improvement were written by 11 women Fig (6.5.2.f). Whilst 9 were happy with the current service, one patient wished the appointment time not to be breached, other women preferred to have a female smear taker.

Fig 6.5.2: Results of the hospital smear clinic user survey

(a) Lunch-time smear clinic feedback

8 women	Yes		No		Unsure
Did we meet your expectations?	**8**		**0**		**0**
If this service was available in the future, would you use it again?	**8**		**0**		**0**
How would you rate this service?	1	2	3	4	5
1 = poor, 5 = excellent	**0**	**0**	**0**	**1**	**7**

(b) Evening smear clinic feedback

23 women	Yes		No		Unsure
Did we meet your expectations?	**22**		**1**		**0**
If this service was available in the future, would you use it again?	**22**		**0**		**1**
How would you rate this service?	1	2	3	4	5
1 = poor, 5 = excellent	**0**	**0**	**2**	**5**	**16**

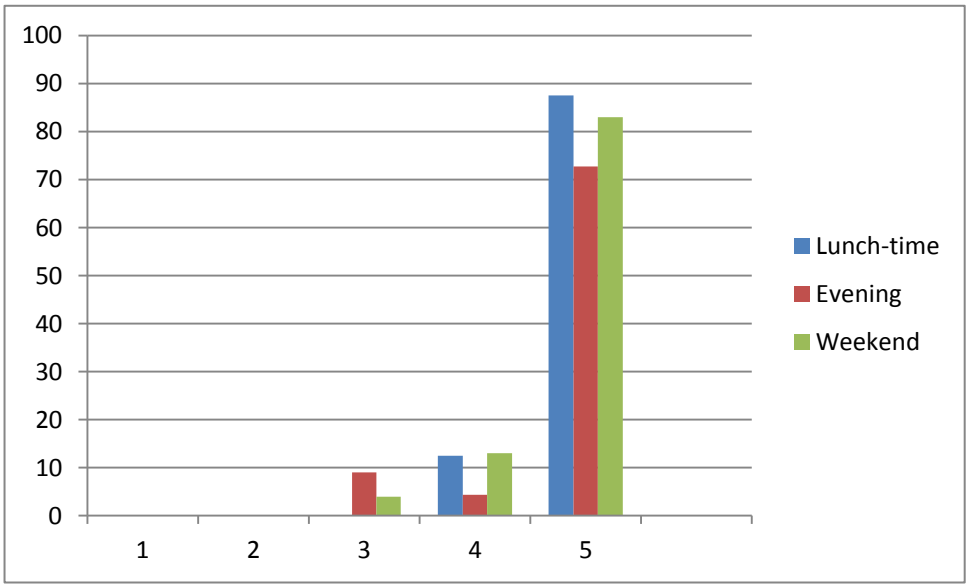
(c) Weekend smear clinic feedback

24 women	Yes		No		Unsure
Did we meet your expectations?	**24**		**0**		**0**
If this service was available in the future, would you use it again?	**23**		**0**		**0**
How would you rate this service?	1	2	3	4	5
1 = poor, 5 = excellent	**0**	**0**	**1**	**3**	**20**

(d) Overall summary of the smear clinic feedback

55 women	Yes	No	Unsure
Did we meet your expectations?	**54**	**1**	**0**
If this service was available in the future, would you use it again?	**53**	**0**	**1**

(e) Overall rating of the smear clinic experience



(f) suggestions for improvement

	Any suggestions for improvement
1	Excellent – would be great if this could continue.
2	Comment- much easier than I anticipated. Doc/Nurse excellent.
3	Smaller instrument.
4	Would have been nice to have been given the option of a female nurse testing smear test.
5	Staff was very understanding.
6	Appointments on time!
7	Exceptional service.
8	Doesn't need improving it works perfect.
9	None.
10	None.
11	No.

Discussion

The size of the questionnaire slip was limited to a 1/3rd of an A4 sheet. The number of questions was limited to 4, designed in this way to keep the woman's focus on the main points. This was also to improve compliance. The main objective of the questionnaire was to use its outcomes for service development.

Most defaulters who asked for a hospital smear clinic appointment in the younger defaulter's study were included in this sample. Some women who selected option 2 in other studies also came to these clinics along with a small number of HPV+ women who came for their smear test.

The hospital smear clinic met all except one out of 54 service user's expectations. All except one would use this service in the future (one person did not answer this question). All except 3 rated this service 4-5 out of a scale of 5, where 5 was 'excellent' and 1 was 'poor'. No serious adverse comment was made by clinic attendees although one woman who was seen on time was not happy about it and another woman would have preferred a female smear taker.

The effectiveness of flexible smear appointments was tested in a population-based randomized trial in western Sweden (Broberg, Jonasson et al. 2013). Telephone contact with non-attendees, offering an appointment to take a smear, was compared with a control group. Of 8,800 cervical screening defaulters, 4,000 were randomized to a telephone arm, another 800 were offered HPV self-sampling and 4,000 constituted a control group. Participation during the following 12 months was significantly higher in the telephone arm group than in the control group, 718 (18.0%) versus 422 (10.6%) (RR: 1.70, 95%CI, 1.52-1.90). However, the difference over a one year period was small (7.4%). 'Out of normal working time appointments' were endorsed by a similar proportion (17%) of 290 women who were likely to be eligible for breast screening when the research focus was to explore aspects of the service likely to increase participation (Richardson 1990). In our studies between 1% and 4% of defaulters chose a hospital clinic for their smear and of those opting for a hospital appointment only 71% actually attended.

Conclusions

The hospital smear clinic was acceptable to defaulters. The hospital 'out of normal working hours' smear clinic was highly rated by its service users. All 3 smear clinics were equally rated. No serious adverse comments were made by clinic attendees.

Running a hospital smear clinic at a frequency which is governed by its demand (e.g. first Wednesday and/or first Saturday of the month) may be recommended. This may widen women's choice.

CHAPTER 7

Discussion, implications and conclusions

7.1 DISCUSSION

7.1.1. High HPV prevalence

Clinical application of vaginal self-sampling for HPV screening was evaluated in most of these studies. We explored potential reasons for not going for the smear test. We also explored what was acceptable for those who did not accept these options to be screened by using Questionnaire 3.

The HPV prevalence in vaginal samples is very high in all of our studies (Table 7.1.1.1), in comparison to the cervical residual samples of those who were tested positive in self-collected samples (Table 7.1.1.2).

Table 7.1.1.1: HPV test results of vaginal samples

	1000 study	200 study	2000 study	Older study	**Total**
HPV + (%)	46%	60%	44%	40%	**46%**
HPV – (%)	54%	40%	56%	60%	**54%**
Total (n)	92	40	107	43	**282 (100%)**

Table 7.1.1.2: Valid HPV test results of cervical smear residual samples in women who were HPV positive in vaginal samples

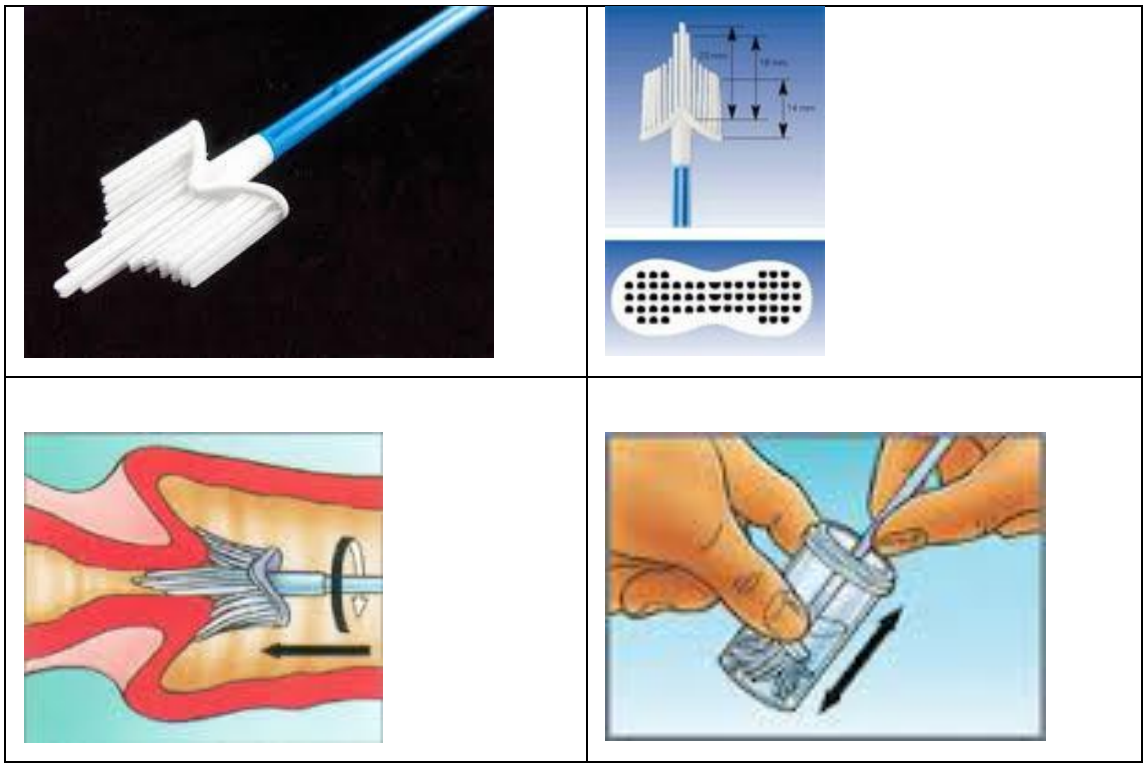
	1000 study	200 study	2000 study	Oder study	**Total**
HPV + (%)	43%	38%	12%	50%	**33%**
HPV – (%)	57%	63%	88%	50%	**67%**
Total (n)	35	16	25	8	**84 (100%)**

All cervical smears were taken adhering to the standard procedure (NHSCSP 2006). Inadequate cervical residual samples giving an invalid HPV result has never been an issue in the 30-56 year age group. However, it caused problems when smear residuals were tested for HPV. It was apparent when smears were collected from older defaulters that the cellular material obtained on the sampling brushes (Cervex brush and endocervical brush) was scanty. Hence, we took extra care to make sure that we suspended as much sample as possible in the ThinPrep vial.

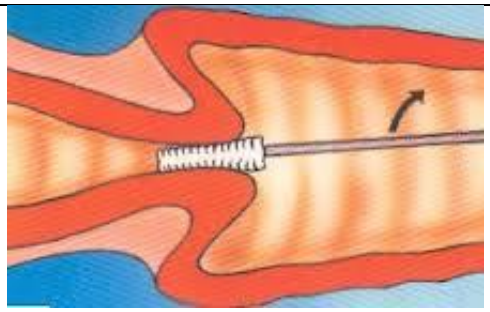
First, the Cervex brush (Fig 7.1.1.1a) was agitated in the ThinPrep vial according to the manufacturer's instructions- the brush head was pushed against the bottom of the vial 10 times, forcing the bristles to bend apart. Finally, it was swirled vigorously to release any additional cellular material. However, this technique was not applicable to the endocervical brush which has very fine, short nylon bristles attached to a metal central helix (Fig 7.1.1.1b) Even though the manufacturer's instructions were followed (the cytobrush was immersed and agitated in the vial containing the liquid medium to release cells), about half of the specimen was left on the brush head due to the thick mucous nature of the specimen. This problem was overcome by rubbing the endocervical brush with the Cervex brush within the PreservCyt medium of the ThinPrep vial (using the Cervex brush to comb the bristles of the endocervical brush). Finally, both brushes were swirled in the liquid medium, before being put into the disposal bin. This technique appears to have left little specimen on bristles.

Fig 7.1.1.1: The cervical sampling technique

(a) with Rovers Cervex® brush



(b) with the endocervical brush



Despite this technique to transfer the sample to the liquid medium, the resulting cervical sample did not appear to be as cellular as the pre-menopausal cervical sample.

A similar trend was seen with samples obtained using an Evalyn brush. Evalyn samples received from pre-menopausal women appeared to contain a rich cellular material. Mucous, cellular material was seen not only on the bristles, but also on the sleeve of the Evalyn brush. However, we did not include material on the sleeve in the PreservCyt medium to minimise contamination. This heavily cellular material which is probably only available with the Evalyn brush (in comparison to other self-sampling devices) may partially explain higher HPV prevalence in these vaginal samples. A good sample is vital for a good result. Not only did the Evalyn sampler collect arguably a very good sample, we also concentrated it to make it even better. Based on results of our first validation study- 'can women self-collect an adequate sample for HPV screening?' it was decided that the ThinPrep samples should be concentrated 4 fold (p.62).

Unlike other nucleic acid amplification tests, the Hologic Cervista HR-HPV invader technology apparently requires a rich cellular sample in order to give a valid result. This appears to be an adaptation to prevent picking up clinically insignificant HPV infections. However, this is less

relevant when it comes to self-sampling, where detection of any high-risk infection may be necessary due to a less cellular nature of the self-collected sample. We wanted to find women with any important high-risk genital HPV infection during the primary screening step. We did not want to compromise the sensitivity of the HPV screening to get reasonable positive predictive value (PPV) as HPV positives were cytology triaged for colposcopy.

We thought that the approach of picking up any significant high-risk genital HPV infection may not do any harm as we would not treat anyone based on the HPV result alone. We considered HPV positivity as a marker of women who would require a smear test, nothing else. We labelled the HPV home test as the 'pre-screening test' and the smear test as the 'proper screening test'. We counselled our study participants accordingly.

The hrHPV prevalence could have been reduced by increasing the cut-off values of the Cervista test. A higher cut-off value may have picked up fewer HPV infections. It is possible that women who have done self-sampling (282/3498=8%) were indeed at a higher risk of having the HPV infection or at least these women might have perceived that. However, lower HPV prevalence in cervical counterparts suggests that other factors may have confounded this result. It can be argued that some HPV results of cervical residuals were falsely negative. It is theoretically possible that Hologic ThinPrep LBC slide absorbs all infected cells in the ThinPrep pot and leaves the residual with an inadequate sample. For example, cervical smear of the patient number 2 of the proof of concept study (Table 3.1.1.) did not have any genomic human DNA and failed the internal control. Presence of inhibitors is another possibility. The answer to this question could have been found, if we had collected a separate cervical sample and tested it. However, we did not originally plan to do this, mainly due to resource implications.

High HPV prevalence was reported in other studies. In their cohort study involving the whole of Scotland, (Kavanagh, Sinka et al. 2013) estimated the HPV prevalence in young women in Scotland in view to monitoring the vaccination impact. The weighted prevalence of any HPV in young women aged 20–21 was 32.2% for the urine, 39.5% for the self–taken swab, and 49.4% for the residual LBC samples. They had used a vaginal swab for self-sampling which might have been the reason for discrepancy of prevalence between the cervix and the vagina. Although this was a younger cohort of women than ours, the estimated HPV prevalence was high.

A self-sampling study that included 878 sexually active women, aged 15-69 (Holanda, Castelo et al. 2006), reported 34% hrHPV prevalence when a brush was used as the self-sampler. The same type of brush was used for clinician a sample which was tested only for HPV (without using it for cytology). The cervical hrHPV prevalence was 29%. The Hybrid Capture II DNA positivity (relative light units in relation to a 1-pg/mL positive control ≥1) was significantly more common in vaginal samples. The hrHPV prevalence remained higher even if the threshold of positivity was raised to RLU/PC≥3. Although we do not have access to such DNA quantification cut-off data, this may well have been the case in our study samples.

Vaginal self-collected samples had slightly higher HPV rates than cervical counterparts, irrespective of the age among the 307 women aged 15-49 years in Canada. (Karwalajtys, Howard et al. 2006). The prevalence of HPV was (64/307= 20%) and (54/307=18%) in the vaginal and cervical specimens, respectively. Among the women aged 50 years and older, prevalence was (15/152=10%) and (13/152=9%), respectively.

A Swedish study (Stenvall, Wikstrom et al. 2007), reported a mean hrHPV prevalence of 26% (30/117) in a population based study conducted in Sweden. Participants were women aged between 35 and 50 years, who had not had a smear test for 6 years. The self-sampling device used was Qvintip. The HC2 was used for HPV testing, which can detect HPV DNA concentrations over 1 pg/mL. The hrHPV prevalence was 31% in women aged 35-42.

Contamination of samples during the initial processing at Dumfries laboratory or during the testing in Edinburgh HPV Reference Centre was also possible. However, this was discussed within the research team soon after the first set of results was available. Although no evidence for contamination was found, potential ways of contamination were discussed and utmost care was taken to prevent contamination. But still, high prevalence was noted throughout the 10 month study period. In some days, only one sample was processed in Dumfries laboratory, making the contamination from another sample virtually impossible.

Most cervical smears were collected 2-3 months after self-sampling. Although up to third of HPV infections may have been overcome by host immune system during such a short period, it cannot be attributed to this major difference in HPV positivity.

Even if every contributing factor was accounted for, the exact reason for very high HPV prevalence seen in these vaginal samples cannot be fully explained. Hopefully, future evidence on the Evalyn brush will inform us more about this.

7.1.2. Response rates

Self-sampling for HPV screening was offered in all except the younger defaulter study. Defaulters who chose options 1 to 5 were considered as positive responses. Defaulter's response depended on many factors.

The 1000 defaulter study was the first study group. Participants were recruited between 15 March and 20 April 2012. The total positive response rate was 24% (236/1000) at six months. About a third (40/129=31%) who did not respond requested a self-sampling kit only after receiving the reminder letter, 3 months after the first invitation letter.

The 200 defaulter study was the second study group. Participants were recruited between 18 and 22 June 2012. The key feature of this study in comparison to the other three was the fact that a self-sampling kit was sent with the initial invitation letter. The total positive response rate was 32% (63/200) at six months. Twenty (10%) samples were received within the first week. Another 11 samples were received in next 3 weeks. The vast majority (34/40=85%) of returned samples were returned within 3 months. Whilst 11 new kit requests were received after sending the reminder letter, one person retuned the kit with a sample in October, which was 4 months after it had been sent to her. Although 11 women responded after the reminder, about 15% (6/40) samples were received after the reminder letter. Most of other options (1, 2, 5, & 6) were ticked and received in the first 2 weeks of sending the initial invitation letter. Basically, the response was immediate and it was comparatively good.

The 2000 defaulter study was the third study group. Participants were recruited between 9th and 13th July 2012 which was 4 months after the database was generated. The total positive response rate was 16% at six months. This cohort of women was sent the reminder letter 2 months after the initial invitation, rather than 3 months in the previous 2 studies. Only 22 out of 158 (14%) requested self-sampling after receiving the reminder letter in the second week in September. Basically, the overall response rate as well as the response to the reminder letter was poor in this cohort.

The majority (57%) of those who indicated they were willing to take up the smear test did not do so within a one-year period (Orbell and Sheeran 1998). This longitudinal test of the association between motivation to undertake a precautionary health action and subsequent behaviour was conducted on women's uptake of the cervical screening test in 166 women who had never been screened.

The older defaulter study was the fifth study group. Participants were recruited between 29th to 31st October. Twenty six samples were received from the letter + kit group and 24 kit requests were received from the letter only group at 2 months. No reminder was sent.

Table 7.1.2.1: Self-sampling response to the initial invitation and the reminder

	1000 defaulter study	200 defaulter study	2000 defaulter study	older defaulter study
Kits requested first round	89 (69%)	34* (76%)	136 (86%)	50 (100%)
Kits requested second round	40 (31%)	1*+11 (24%)	22 (14%)	N/A (0%)
Total (n/N%)	**129/1000 (13%)**	**46**/200 (23%)**	**158/2031 (8%)**	**50/584 (9%)**

*kits sent in the first cycle, ** number of kit requests received from the first cycle + 11 samples that were requested in the second cycle.

A significant heterogeneity with two degrees of freedom is observed between 3 response rates in these three studies (1000, 200, 2000 studies) conducted in the same 30-55 year age group database (X_2^2=54.7, p<0.001). It appears that the self-sampling response to the initial invitation was 2% lower than its comparable counterparts. The self-sampling response rate to the reminder was lowest (14%) in the 2000 defaulter study group. Several factors may have affected the lower response rate seen in the 2000 women study group.

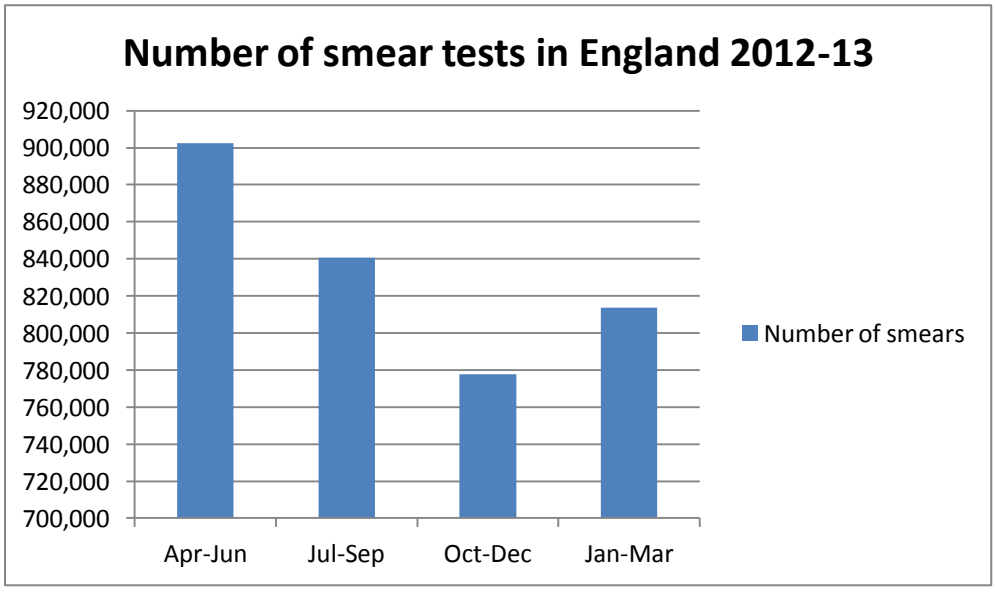
Addresses of the 1000 and 200 women study groups were cross-checked against the hospital database, TOPAS. When in doubt, telephone calls were made by the data manager of the Research and Development Department. Consequently, 246 out of 1246 in the 1000 study group and 21 out of 221 in the 200 study group were removed from the list. About 18% that were found on the SCCRS appeared to be inaccurate. Documented reasons for removing

defaulters from the list were numerous. The most common category was not living at the current address, which was explained as 'untraceable', not living in Dumfries & Galloway, not living in Scotland, living in elsewhere in UK, living in a foreign country, not registered, change of address and 'no fixed abode'. There were names of 5 deceased women in that list of 1467. According to the younger defaulter study, up to 8% addresses of younger defaulters found in the SCCRS could have been inaccurate.

Finally, members of the research team who ran the smear clinic observed that screening uptake was poor during school holidays and during the time that London 2012 Olympic and Para-Olympic games were being held. I believe that these activities in the summer might have negatively impacted the screening uptake rate of the 2000 defaulter study which was conducted at the same time. This trend was seen nationally.

A total of 3.3 million cervical smears were carried out in England in 2012-13 (N=3,334,052) (Fig 7.1.2.1). The number of smears carried out in the second quarter (July to September, n=840,525) was significantly less than that of the first three months (n=902,426) [RR=0.9, 0.9-0.9]. It dropped by another 10% in the third quarter from October to December (n=777,594) [RR=0.9, 0.9-0.9]. Interestingly, the reduction of screening uptake rate seen in our studies over the time follows the same pattern.

Fig 7.1.2.1: Number of smear tests carried out in each quarter in 2012-13 in England



Source: Health and Social Care Information Centre. (2013)

The average monthly smear uptake rate among defaulters (without any intervention) may be considered as 1% across our study population. It was 0.78% per month, in the control group older (56-60 years) defaulters (6÷12÷64). It was 1.15% (119÷6÷1732) in the historical control group. It would have been 1.38% per month (58÷6÷720) (61÷6÷721) in the younger (20-29) defaulters predicted control groups. The mean monthly smear uptake in the middle-aged (30-55 years) group (n=3498) of defaulters is likely to have been in between these two figures, which can be rounded up to 1% per month.

Self-sampling uptake rates in different study groups

The self-sampling uptake rate of our studies (Table 7.1.2.2) can be put in to perspective when other population based studies are considered. It is best to compare the self-sampling uptake rate, as it was the measured primary outcome in most of the other studies (Table 1.2.3).

Table 7.1.2.2: Self-sampling uptake rate to the initial invitation and the reminder

	1000 defaulter study	200 defaulter study	2000 defaulter study	older defaulter study
Samples received after the initial invitation	71 (77%)	34 (85%)	95 (88%)	43 (100%)
Samples received after the reminder	21 (23%)	1*+5 (15%)	13 (12%)	N/A (0%)
Total n/N (%)	**92/1000 (9.2%)**	**40/200 (20.0%)**	**107+1/2031 (5.3%)**	**43+1/584 (7.4%)**

*a kit which was sent out after the initial invitation

In many aspects, our study is best compared with the London study (Szarewski, Cadman et al. 2011). The main differences between these two studies were population, self-sampling kit and the approach. The population in Westminster is multi-cultural and more mobile in comparison to Dumfries & Galloway. Whilst these factors are not in favour of higher screening uptake by defaulters, the lower smear coverage (68% in London, 77% in Dumfries) should have been in favour of taking up self-sampling. The London study (Szarewski, Cadman et al. 2011) used a small Dacron swab as a self-sampling kit with the invitation letter and other paperwork. Apart from the self-sampling kit, list clearing, multiple options list and the reminder, the method of intervention of the London study appears similar to our 200 defaulter study. However, self-sampling uptake rate in London was lower (96/1500=6.4%) than our 200 defaulter study

(20.0%). Even if the first cycle alone is considered, the self-sampling uptake rate of the 200 study group was 35/200= 17.5%. But, the self-sampling uptake rate of the 56-60 age group in our study was lower (26/292=8.9% in the 'kit' method) than that of the 200 defaulter study group. Confounding factors for lower screening uptake in the older defaulter study could have been the extreme end of the screening age group and the time of year that the study was conducted (winter 2012). Perhaps, differences in approach may have made a difference to outcomes. Whilst we made an open invitation for defaulters to come back to screening by giving them as many options as possible, one arm of the London study offered self-sampling only. However, the overall self-sampling (which mostly includes the 'letter' method) uptake rate of our study's total population 7.4% (284/3815) is similar to the London study.

A recently published study (Darlin, Borgfeldt et al. 2013), targetted 1500 defaulters aged between 32 and 64 to be randomised 2:1 to self-sampling and a flexible no-fee appointment for a cervical smear. The study design of this study was similar to that of our 200 defaulter study. However, there were some differences. Participants had not been to a screening in over 9 years. The self-sampling kit was a cotton swab. One month after the invitation, a reminder was sent to non-responding women with another self-sampling kit.

A total of 147 (15%) samples were received, of which two thirds (93) were received after the reminder. Only 10/147 (7%) were hrHPV positive. A very low number of women (21=4%) opted for a smear test, of which two thirds (14/21) requested it after receiving the reminder letter. The screening uptake rate in the first round of this study was surprisingly low (5%), in comparison to many Swedish studies which reported self-sampling uptake rates of 31.7%, 39.0%, 39.0, 39.1% and 39.4% (Table 7.1.2.2). The mean self-sampling uptake rate of our study groups which were sent a reminder was 7.4% (240/3231). The longer interval between the last screening test and the current multiple screening choices offer should have been the most important negative factor affecting screening uptake of the (Darlin et al. 2013) study. However, the mean duration since the last smear test our 200 defaulter study showed was 7 years, with 3 women who had never been to screening. This duration was 9 in the 1000 defaulter group and 8 years in the 2000 defaulter group. Perhaps the appearance of the Evalyn brush which appears to simulate the smear collection technique may have given women better reassurance than a cotton swab. Only 3 out of 249 Evalyn brush users in our study were unsure if they had collected an adequate sample.

7.1.3. Effectiveness of HPV screening methods

The relative effectiveness of HPV self-sampling against the routine cytology screening was measured in some self-sampling studies. A Swedish study by Lindell recruited 3,618 women aged 50-65 years for self-sampling and they used 6,048 women of the same age as controls. Whilst 15 CIN2+ were diagnosed in controls (0.25%), HPV self-sampling for HPV screening arm diagnosed 10 CIN2+ in 1426 self-samples (0.70%). The odds ratio for using self-sampled vaginal smear and a high-risk HPV test for detection of CIN2+ when compared with Pap smear for detection of the same lesion was 2.84 (95%CI, 1.14–6.77, P = 0.0174).

The London study Szarewski et al. (2011) diagnosed 3 CIN2+ (CIN2, CIN3 and cancer, each) in 96/1500 (6.4%) self-samples, whereas one CIN2+ was found in 68 (4.5%) women who attended for smears out of 1,500 controls, indicating that the HPV screening appears more sensitive than LBC in detecting CIN2+, although numbers are too low to draw any reliable conclusions.

The MARCH Trial demonstrated an odds ratio of 3 between HPV screening in self-collected samples and the conventional Pap smear. About 10% (884/9202=9.6%) who self-collected were HPV positive. There were 108 (1.2%) CIN2+ in this unscreened Mexican cohort. HPV testing identified 117·4 women with CIN 2 or worse per 10 000 (95·2–139·5) compared with 34·4 women with CIN 2 or worse per 10 000 (23·4–45·3) identified by cytology; the relative sensitivity of HPV testing was 3·4 times greater (2·4–4·9). Similarly, HPV testing detected 4·2 times (1·9–9·2) more invasive cancers than cytology did (30·4 per 10 000 [19·1–41·7] versus 7·2 per 10 000 [2·2–12·3]).

Although 383 defaulters opted to self-collect, only 284 (74%) samples were received. Almost all, 118/130 (91%) HPV positives had smear tests. Three of them were high-grade smears. They were referred to colposcopy. All of them were diagnosed to have CIN2+ on LLETZ (2x CIN3 and 1x CIN2). HPV positive but smear negative 67 defaulters had colposcopy and a repeat smear 12 months after the first. Whilst 1 woman had a high grade smear result (one CIN2+) at the annual follow-up, 4 defaulters had hgCIN on colposcopy (four CIN2+) despite negative smears. HPV screening in self-collected samples appears to be more sensitive than cytology screening in detecting CIN2+. Findings of this annual follow-up were consistent with previous self-sampling evidence (Lindell, Sanner et al. 2012; Tamalet, Le Retraite et al. 2013).

The HPV prevalence in our 30-60 year age group was 130/282=46%. There were 3 CIN2+ in the first round and 5 CIN2+ in the annual follow-up of HPV+, with a total of 8/282=2.7%. Reported rates of CIN2+ in 11 population-based self-sampling studies were between 0% and 3% (Table 7.1.2.2), indicating that the effectiveness of our self-sampling methods is comparable to other self-sampling studies. A pooled analysis of 5 self-sampling studies conducted in China reported a higher percentage (507/13,004= 3.9%) CIN2+ (Zhao, Lewkowitz et al. 2012). However, participants of these studies were referred to colposcopy, if any of the multiple cervical screening tests (self HPV, cervical HPV, LBC, VIA) were positive. Four random biopsies were taken from each quadrant of the cervix from everyone who attended colposcopy, which tended to increase the number of CIN2+ cases diagnosed.

Most women (51/77=71%) who ticked option 2 came for a smear test at the hospital smear clinic, two of them had a borderline smear result and 1 smear had to be repeated due to an unsatisfactory result (inadequate sample). One woman who requested a self-sampling kit could not be HPV screened, as no kit was received. She eventually came for a smear test, which was reported as moderate dyskaryosis and was diagnosed as CIN3 on LLETZ. A total of 350/1441 (24%) in the younger defaulters' study had been to cervical smears in 13 months. Five percent 19/350 of them had had an abnormal (BNC+) smear result. All 12 women who were referred to colposcopy had attended colposcopy. A total of 11 (3.1%) CIN2+ (five CIN2, five CIN3 and one CGIN) were diagnosed in these 350 defaulters aged between 20 and 29 years of age.

Of the 153 HPV negative women, 12 had cervical smears in the community, in the following 12 months. One of them had an abnormal smear result.

7.1.4. Communication of results

Results were sent to participants in writing within 2 days by first class mail after being made available (please see the results letters in Appendix 2). Multiple identifiers such as community health index (CHI) number, date of sample collection, date that the sample was received and the lab reference number were included to make it more reliable (trustworthy) to the participant. It was assumed that mistakes could be minimised by adopting this strategy. We are very pleased to report that no mistakes were made in communicating results.

We were very careful when drafting the results letter, in order to make it clear, concise and simple. Whilst emphasising the importance of follow-up, we wanted to make sure that the letter

would not cause unnecessary anxiety. We included several ways that participants could contact different levels of healthcare professionals for any further information or advice. This letter was reviewed by several healthcare professionals and appropriate changes were made.

We wanted to make the HPV positive letter (Fig 8.2.15) clear and straightforward. It is a dual purpose letter- to deliver the result and offer the follow-up appointment, which is similar to a colposcopy clinic appointment. We decided not to include the word cancer, which could cause unnecessary anxiety. We made the concepts of HPV and cytology screening simpler by phrasing “positive for HPV infection means that you need to have a smear test”. This letter was accompanied by a comprehensive 2 page list of frequently asked questions (Fig 8.2.15, Appendix 2).

Drafting the HPV negative results letter was much harder than its positive counterpart. It was difficult to find the right balance between being honest about the HPV negative result and emphasising the importance of accepting the next smear test which was due in 0 days to 2 years after receiving this letter. However, we adopted a pragmatic strategy. First, we said that this result may be falsely negative. Second, although a woman could be negative today, she may acquire the disease in due course. Thirdly, a smear would give more reassurance. We developed this letter (Fig 8.2.16, Appendix 2) based on the content of the National Screening Programme’s screening negative result letter.

Four Evalyn samples did not give a valid result in the Cervista first run, and therefore had to be re-tested. Consequently, the HPV result of a 31 year old woman was delayed more than 6 weeks, which caused significant anxiety. This woman’s sample was received the day after one batch of samples had been despatched to Edinburgh. This sample had to wait another 13 days in Dumfries. The sample gave an invalid result due to a problem with the internal control, which had to be repeated. Soon after, the Scottish HPV Reference Laboratory was physically shifted to Edinburgh Royal Infirmary from the medical school building. When they re-established on the new site, the sample was retested. However, it was not possible to test samples due to technical failure of the new Cervista platform until industry experts eventually repaired it. In the seventh week, the participant contacted us. A big apology was rendered. The patient was offered an immediate smear test for which she attended the following morning. The HPV result (negative) was available in the same afternoon, and was communicated over the phone followed by a letter (with a written apology). This is the only result that breached the 6 week

agreed target. Almost all other results were sent to participants within 4 weeks. It was a mistake not to communicate with the patient regarding this delay, which may have alleviated her anxiety.

7.1.4 Communication with participants

We received about 30-40 telephone calls relating to the study. Most informed us that they didn't need cervical screening as either it has not been indicated or they had been to a smear test recently.

Some women were not happy that they received the reminder letter even after they had been to a smear test at their GP practice recently. Some such women became angry when they read the first question of the Questionnaire 3- "Reasons why I declined the testing". The Clinical Governance Department received some phone calls complaining about this, as they had not declined testing. Some women were worried that their smear result or sample may have been lost and that they would have to go for another smear test. Fortunately, these women called either their GP or us.

A person who was sent 2 reminders made a complaint about this study. We were advised by the NHS authorities not to send more than one reminder and to objectively reflect on that incident and learn from it.

7.1.5 Reasons for defaulting

Reasons for defaulting were gathered in various forms at different stages of the study. Reasons for defaulting were mainly collected from women who had opted for screening. These defaulters were more likely to have a practical barrier to overcome, in order to come back to screening. Such reasons were reflected in the questionnaire survey as well as in the qualitative study.

We were able to gather reasons not only from defaulters who wished to come back to screening, but also from those who declined it. Exploring reasons for non-attendance from defaulters who refused further screening despite these multiple, flexible options were possible in 4 ways:

a) as they returned the pre-paid options list
b) when they contacted us through telephone, email and mobile text
c) as they returned the pre-paid questionnaire-3
d) through their carers or healthcare professionals

Gathering and reporting this information was useful for service development. Whilst most of these defaulters did not need cervical screening (e.g. total hysterectomy, disabled who has never been sexually active), some needed it.

A wrong address or the woman no longer being eligible for cervical screening at that address (e.g. women who is living abroad) belong to a separate 'iatrogenic' category. These women were wrongly labelled as defaulters. Deceased individuals also belong to this category. Though the cancer risk of this category would not be reduced by these smear recalls, they are not necessary. It appears that some system should be put in place to clean the call-recall database. This will not only save resources, but also build public confidence in the screening programme, as it would ensure clean and accurate statistics.

7.1.6 Analysis of the written content of the hospital smear clinic consultation

Direct quotations of 'the main reason for not having the last smear test' was recorded in the clerking sheet of the hospital smear clinic. This question was asked soon after women had competed the questionnaire-2, which contained objective questions regarding non-attendance. This may have 'primed' and 'probed' these women's minds to determine the main reason. Hence, most women gave the main reason, promptly. Some women required more time to provide a response. Only a few need to be prompted. No one said "I've never thought about it".

This question was asked by a male gynaecologist (PI), which might have confounded the answer to a minor degree in some women. However, most women gave their reason without any hesitation. Even when embarrassment was the reason, it was more due to a 'familiar health professional' rather than a 'male doctor'.

7.1.7 Annual follow-up

It was agreed that HPV positive women who attended the smear test in the first round would be called to attend the annual follow-up clinic.

7.1.8 Passive follow-up

Will HPV negative defaulters attend future cervical smears? To find the answer for this important question, screening histories of all study participants who were tested negative for HPV (n=153) have been checked on 27 December 2013, 12-18 months since they have

received a negative HPV result. The control group was women (n=99) those who have asked for a kit, but no sample was returned.

A total of 37 women who have had a negative HPV result have been recalled by the SCCRS, 5 (14%) of them have had smear tests. By contrast, 6/34 (18%) in the control group have had a smear test.

This 14% figure looks very positive. These defaulters have been to smears despite the fact that they had a negative screening test within 6-12 months. Furthermore, they were told that they were tested negative for the virus that can cause cervical disease. Even then, 14% were motivated to have the smear test, which testifies the quality of the participant education component of our study. This indicates that this proportion is likely to grow with time as most women believe that they don't have to undergo screening, not more frequent than every 3 years. We promoted screening, not HPV testing. Consequently, women appear to have received a clear, positive message about screening, which may have motivated these HPV negative defaulters to accept the screening recall. If we were to randomise HPV only arm (50%) and smear only arm (50%) for a RCT, we could have struggled to counsel participants properly. Although we wanted to conduct our studies as robust as possible, as clinicians, we were ethically bound to select the right balance for our population.

After receiving the self-sampling kit, 12 women have contacted me to discuss the most suitable cervical screening test for them. Based on the discussion, more than half of them have decided to get a smear test. This may have contributed towards slightly high rate of smear uptake in the control group.

It may be argued that defaulters who decided to self-collect vaginal sample with the Evalyn brush may not participate in future cervical screening. This argument makes sense as most of defaulters who accepted self-sampling did so, as they did not like the smear test in the first place. However, this is not entirely true. We were very conscious about this fact at the beginning of our study. Therefore, we focused on this matter in our participant education component. We emphasised the importance of regular screening and stated that this is a one-off study; hence they may not get the chance to self-sample again. We warn them that if they did not accept the cervical screening recall invitation, they will be put back to the defaulter state, which will result in no recall for another 2½ years. They were told in the results letter that no screening test is 100%

accurate, but, if you were tested negative repetitively, your chance of developing cervical cancer will be very low. The primary aim of our effort was to bring defaulters back to regular screening.

About 1 in 7 defaulters who were tested negative for HPV had responded to their next cervical screening recall, even when they were called within a few months of receiving a HPV negative result. This proportion is likely to grow over the time. This indicates that our efforts of bringing defaulters back to regular screening have been successful.

We will be monitoring this screening uptake rate in the future.

7.1.9 Things which we would have done differently

In our multiple screening options studies, if participants did not respond by 2-3 months, one further reminder letter was sent. However, we were unable to check the screening status of participants before the reminders were sent due to logistical reasons. This sometimes clashed, if the person had been for a smear independently and had not informed us (the research group).

Conducting a second run of main studies in 2013, which is one year after the first intervention, in the same population would have been interesting. However, we were given a target of 31 December as the final date for these studies. If these multiple screening options were offered until 31 March (when national statistics are calculated), the screening coverage in the region could have been much better.

I now feel that we should have included a larger non-intervention (control) group, representative of the whole population, in order to demonstrate robust statistically significant difference. I believed that everyone should be given an equal opportunity to know the potential risk associated with not being screened and have the privilege of make use of using these alternative screening options. Therefore, we limited the control group to a minimum (1% of the total population).

7.1.10 Limitations of these studies

It was difficult to foresee every potential issue that may arise within the study when the study was planned in early 2011. Available resources were another main limitation, as it was virtually nothing at the beginning apart from the support received from the Research & Development Department. Some more interventions, if planned, would have given better answers. One of

them is to offer colposcopy for a representative sample of HPV negatives. This should have given the evidence to support the true negative predictive value of HPV screening.

The high HPV positivity seen in the self-collected material and the discrepancy of HPV positivity that was seen between the self-collected material and cervical smear residual of the same population could have been explained, if a reference HPV test (e.g. HC2 or a highly sensitive PCR-based test) was used for all samples head to head with the Cervista test. However, the Scottish HPV Reference Centre has an excellent quality control programme. Not knowing the cervical HPV status at the annual follow-up visit was another limitation. If a separate cervical sample was taken for HPV testing, it would have given us better answers for some questions such as, high prevalence of HPV in vaginal samples and explaining smear negative but CIN positive cases. However, the associated cost was an issue, as we did not have any funding for this research. Our valued sponsors kindly recognised the importance of this study and supported the essential work proposed.

Despite all of our efforts to get defaulters engaged, the majority of them have not responded. Views, attitudes and behaviours of those defaulters could not be assessed; which was the main limitation of our survey carried out amongst defaulters who did not respond to our options. This has always been the case in other research conducted in this area. It is very important that we understand this limitation as overenthusiastic efforts of getting defaulters into screening may affect patient's/ individual's autonomy. Individual's autonomy must be respected all the time which is a fundamental ethical principle.

The positive response rate in the 2000 study group is less than that of the 1000 and 200 defaulter studies (24-32%) although they are from the same age group (30-55 years). Figures are much lower when it comes to the proportion of self-collected samples received. It was 5.3% (108/2031) in the 2000 study, 9.2% (92/1000) in the 1000 study and 20.0% (40/200) in the 200 study. It could be argued that the self-sampling uptake rate is low in 1000 and 2000 studies. However, the method of recruitment to 1000 and 2000 studies was a letter, whilst it was a kit in the 200 study, which explains some of these differences. The only one previous study which adapted this 'letter' method where a self-sampling needs to be ordered (Giorgi Rossi, Marsili et al. 2011) reported a self-sampling uptake rate of 5.8%. Moreover, there was no 'list clearing' in the 2000 study. This is not a normal cohort of the general population. This is a minority of the population which did not accept screening in the first place. These uptake rates need to be put

in to perspective. Without any intervention, about 1% of these defaulters would go back to screening per month (6/64 per year, 21/1441 per month), according to our controls.

We could have randomised the whole target population into four different intervention arms as Giorgi Rossi and colleagues did (Giorgi Rossi, Marsili et al. 2011), which could have enabled calculate the relative effectiveness of each method. However, I was concerned that such approach could cause issues when getting the ethical approval. For example, encouraging women to take up self-sampling without putting due emphasis on cervical smears may put some members in the ethical committee off.

The non-interventional (control) group consisted only of women aged between 56 and 60 years, which is not ideal. I did not have access to the database that was used to recruit women for the 1000, 200 and 2000 defaulter studies. However, databases that I had access to (older and younger defaulter studies) were randomised appropriately.

Three women who attended smear clinic following a positive HPV test were found to be significantly anxious, which we recorded in the notes. However, it would have been better to formally assess the level of anxiety of these women which will aid planning future research and making some remedies to reduce it.

7.2 Translation of this research into practise

How can these results be used to improve patient care, delivery of services and/or population health?

7.2.1 Potential ways of increasing the screening attendance

We hope that more flexible cervical screening options will be welcomed by non-attendees. We believe that the HPV self-testing gives women privacy and autonomy, empowering and making them full partners of their gynaecological health.

The Scottish Cervical Screening Programme makes an annual estimation of cervical screening coverage based on screening statistics on 31 March in each year. Out of 15 Health Boards, Dumfries and Galloway was the 4th best cervical screened health board in Scotland in 2012 and it is the 3rd in 2013. It became the best cervix screened health board amongst all the mainland boards.

The Scottish cervical screening coverage dropped almost by 2% from 73.0% in 2012 to 71.2% in 2013 (Table 7.2.1.1). The lowest drop is seen in Orkney (0.4%). Second best is Dumfries and Galloway (0.5%) The screening coverage in Dumfries and Galloway was 76.6% in 2011 and 76.1% in 2012. Therefore, Dumfries and Galloway recorded the second best screening uptake rate in Scotland in 2012-13.

Screening coverage is the proportion of the balance between screening attendance and the non-attendance out of the total eligible population. Whilst many non-attendees were going back to screening, more number of usual attendees may have defaulted which has caused this national drop of screening coverage by 1.8% in just one year. The difference between these two was second lowest in Dumfries and Galloway (0.5%) and lowest in both Lothian (2.1%) and Greater Glasgow (2.1%). Although our study interventions may have had some positive impact on these screening outcomes, it cannot be attributed to all of it.

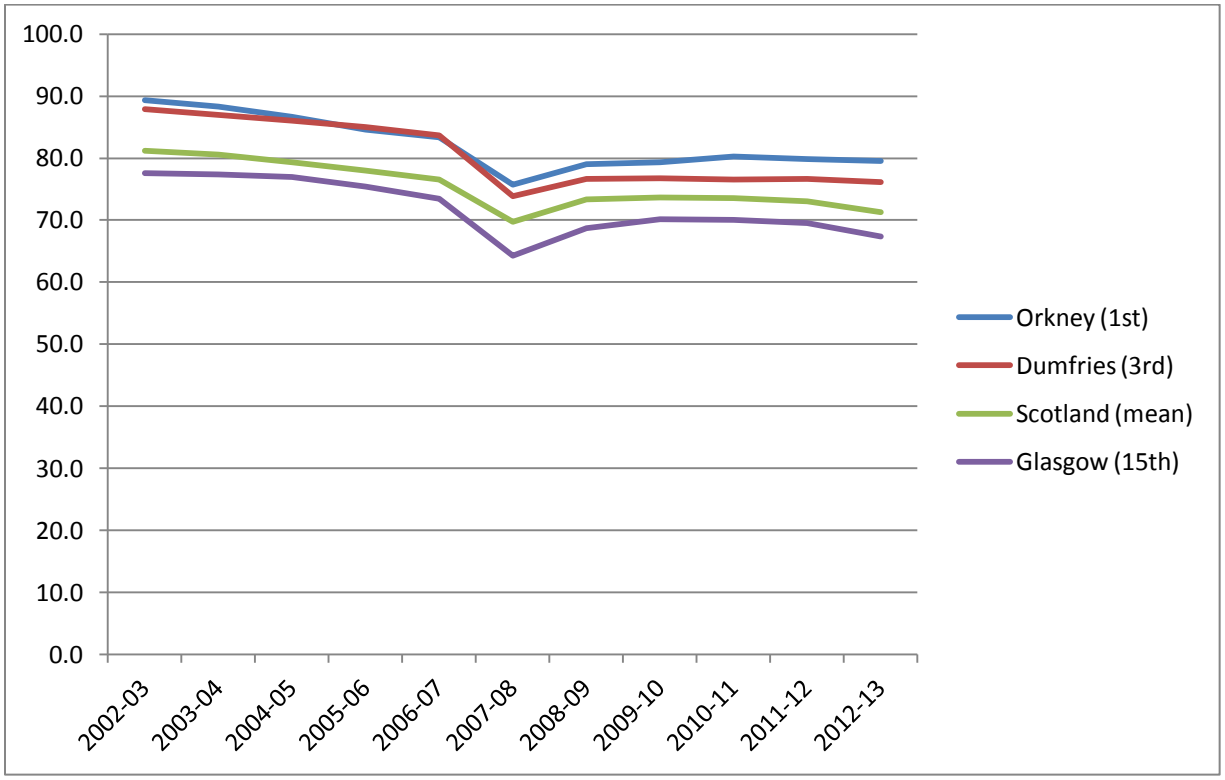
Table 7.2.1.1 Scotland's cervical screening coverage in the last decade (ISD Scotland 2013)

Uptake for Cervical Screening by Health Board: Scotland, 31st March 2003 to 31st March 2013

Percentage uptake of females aged 20-60[1] who had a record of a previous screening test taken within last 3.5 years

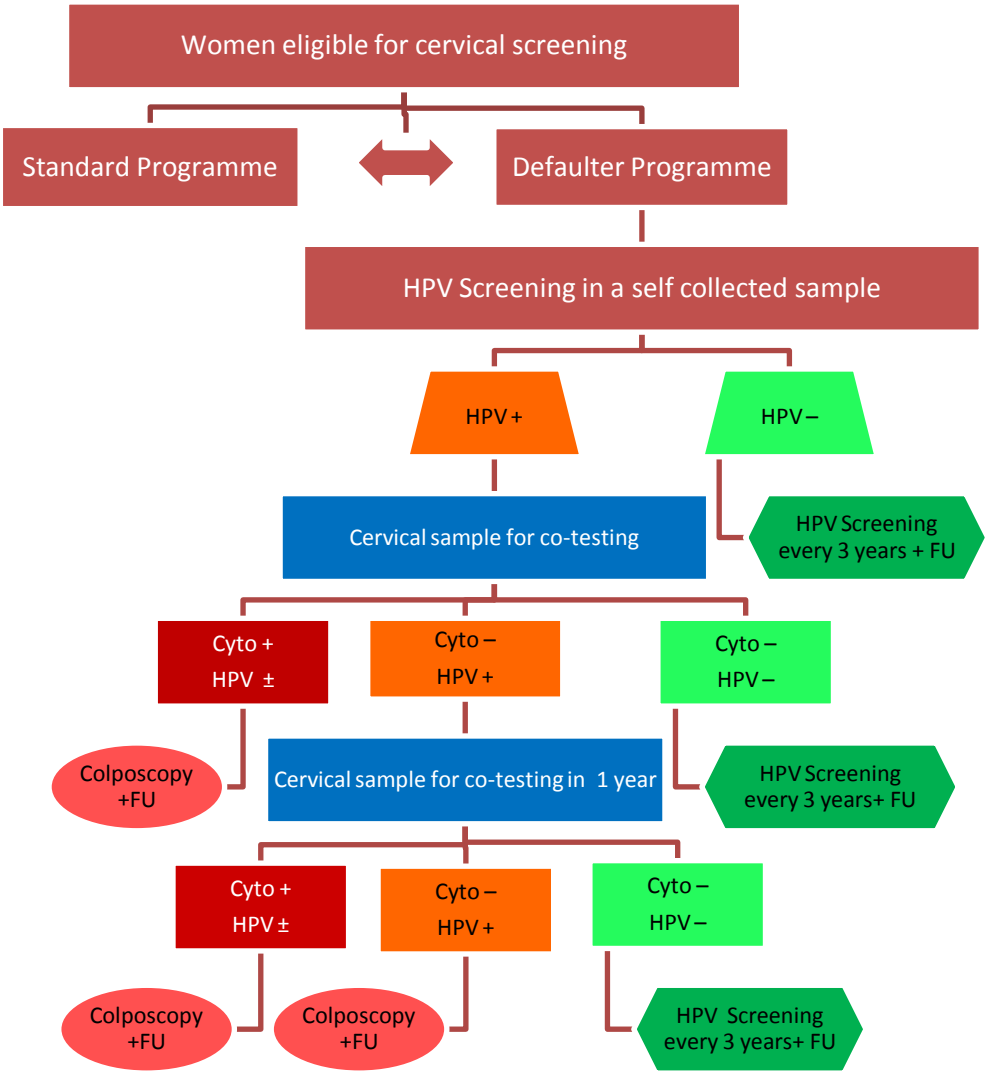
NHS Board of Residence	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13
Scotland [2]	81.2	80.6	79.3	78.0	76.5	69.7	73.4	73.7	73.6	73.0	71.2
(Former) Argyll & Clyde*	79.8	78.8	77.6	76.2	74.8	67.1	72.4	74.2	74.6	74.2	72.7
Ayrshire & Arran	83.8	82.4	80.9	79.5	78.3	70.4	75.1	75.6	75.3	74.7	73.0
Borders	87.2	86.8	86.5	85.7	84.6	75.8	78.4	78.4	77.9	77.0	75.2
Dumfries & Galloway	87.9	87.0	86.0	85.0	83.6	73.8	76.7	76.8	76.6	76.6	76.1
Fife	78.6	78.4	77.0	74.9	73.2	71.2	73.8	72.6	72.6	72.1	70.8
Forth Valley	81.7	80.7	79.4	77.6	77.5	75.5	76.8	76.2	75.1	75.0	73.0
Grampian	84.6	84.0	82.9	81.4	79.7	72.2	75.7	76.1	75.9	75.3	73.5
Greater Glasgow*	77.6	77.4	76.9	75.4	73.5	64.2	68.7	70.1	70.1	69.5	67.4
Highland*	85.3	84.7	83.7	82.8	81.7	71.4	75.8	76.5	76.4	75.9	74.2
Lanarkshire	80.6	79.9	77.8	77.5	76.6	67.9	72.6	74.0	73.9	73.7	72.4
Lothian [3]	81.2	80.7	79.7	78.6	77.4	70.3	73.1	72.5	72.5	71.3	69.2
Orkney	89.3	88.3	86.7	84.6	83.4	75.7	79.0	79.3	80.2	79.9	79.5
Shetland	88.7	88.8	87.6	86.3	85.8	77.9	81.4	81.0	80.6	80.1	78.2
Tayside	80.6	79.2	76.8	75.1	73.5	72.5	75.0	74.2	74.0	73.3	71.8
Western Isles	84.4	83.7	82.5	82.7	79.8	70.8	74.0	74.7	74.7	74.1	72.6

Fig 7.2.1.1 Scotland's cervical screening coverage (%) in the last decade



Developing more flexible and convenient cervical screening options will be a continued process, based on findings of this study. We hope that other screening programmes may adapt this flexible approach which tends to improve the compliance and hence, the coverage.
At the end of this study, we designed a 'screening service model' (please see Fig 7.2.1.2) that could be replicated among other health boards. We may be able to increase the cervical screening coverage and hence, to reduce the cancer incidence, morbidity & mortality. Offering self-testing may be cost-effective. This may be the introduction of dual method testing for cervical screening within the NHS so as to include a defaulter screening programme.

Fig 7.2.1.2: Proposed screening model



Recognising self-sampling for HPV screening as a primordial screening test (a test which tells you who should be further screened) will be an important step forward, at least for getting defaulters back to the standard screening programme. Over 90% of vaginal HPV positives in our study have come for the smear test, which they would have refused otherwise. A gold standard primary screening test which will have an excellent sensitivity and specificity can be carried out subsequently using a proper sample. It is not very realistic to expect the same sensitivity and specificity from a woman collected sample from currently available self-sampling devices. However, evidence suggests (Arbyn, Verdoodt et al. 2014) that current methodologies are good enough to recognise women with genital HPV infection. Once women find that they are at higher risk of developing disease, they will come forward for further testing. Recognising self-sampling for HPV screening as a primordial cervical screening test will reduce unnecessary anxieties about screening, which may enhance compliance. We adapted this approach in our study which has been accepted by almost all of participants.

Other medical screening programmes use various samples other than the gold standard screening test. Such examples are:

1. saliva and urine sample for HIV screening rather than serum
2. identifying fecal occult blood in bowel screening rather than sigmoidoscopy

Some screening programmes use a combined risk score in defining individuals at risk. Such examples are:

1. Pregnancy's Down syndrome (DS) risk is usually calculated using woman's demography (age), several serum markers and some ultrasound markers, in combination. For example, maternal age at the expected date of delivery; serum β human chorionic gonadotropin (βhCG), alpha feto protein (AFP), unconjugated estriol (uE3), Inhibin A in the second trimester (15 weeks); pregnancy associated plasma protein-A (PAPA) at 10 weeks and nuchal translucency scan 11-14 weeks gestation are all included in the integrated screening for DS. The risk of DS is calculated by multiplying the background maternal age and gestation related risk by likelihood ratio derived from the nuchal scan and blood test results of two stages.

Such a complex integrated test for Down syndrome screening has been deveoped mainly for one purpose- to increase the accuracy of the screening test. This test seems to be cost-effective (Wald, Bestwick et al. 2006) considering the the lowest false positive rate (1-2%) and higher

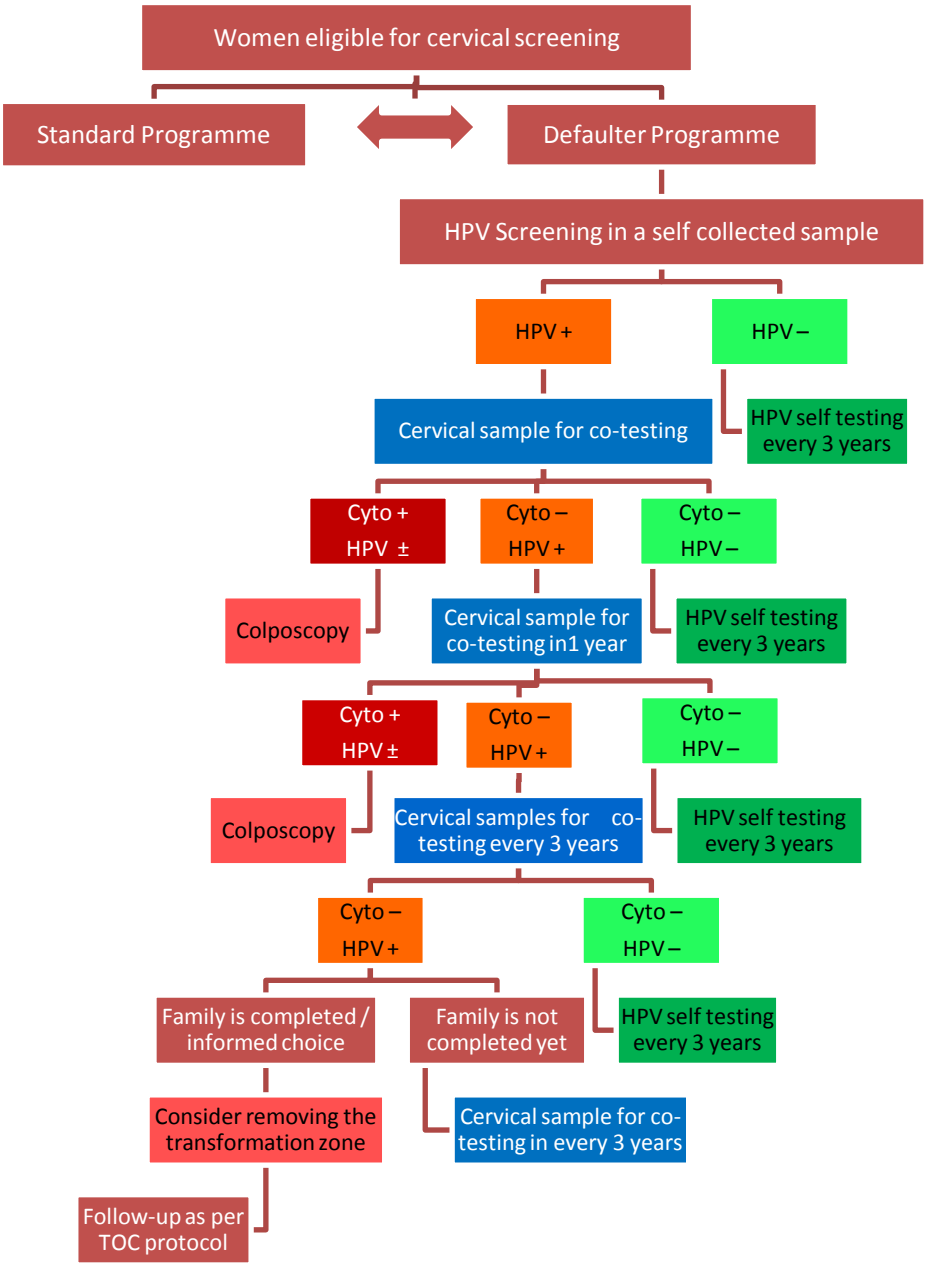
sensitivity (85-90%) amongst 6 screening tests which have sensitivities between 60% and 90% (Gekas, Gagne et al. 2009; Wald, Huttly et al. 2009). Whilst many NHS organisations offer this to the public (Wald, Bestwick et al. 2006), others still offer the double test which has the sensitivity of 60% for a given false positive rate. Considering the seriousness of the cervical cancer, it would be reasonable to make the HPV self sampling as a primordial screening test.

Therefore, it is necessary give the self sampling for HPV screening the place that it deserves- primodical screening test. If we attempted to replace the current primary screening test, it may not work. It appears that using HPV status of the self test in combination with the cervical cytology ±HPV testing may lead to confusing results. Therefore, it is best to consider the self collected HPV test as the test to tell whether or not a defaulter needs a cervical smear test (Fig 7.2.3). This approach may reduce any conflicting opinion and build good public understanding about it.

7.2.2 Proposed colposcopy management pathway

There is no established professional consensus on how to manage HPV screen positive women. For the management of women with persistent cervical HPV infection, the following colposcopy management pathway (Fig 7.2.2.1) can be suggested.

Fig 7.2.2.1: Proposed colposcopy management pathway for HPV screen positives



Abbreviations: Cyto- = normal liquid based cytology; Cyto+= BNC+; TOC= test of cure.

Women with cervical cancer in the post-screening age group present relatively late with more advanced disease than the screen-detected cancer, which is the most apparent reason for increased risk of mortality observed in the elderly. However, it is possibly associated with poor immunity, with consequent reactivation of HPV infection contributing to this sharp rise in the age specific mortality rate. The cause of poor immunity may be associated with lack of estrogen. One randomised controlled trial (Sawaya, Grady et al. 2000) and a case control study (Parazzini, La Vecchia et al. 1997) found that there is no increase in relative risk from the use of systemic HRT. This highlights the importance of studies examining effects of HRT, both systemic and locally administered estrogen, on cervical neoplasia which may suggest a novel way of cervical cancer prevention.

7.3 Public Engagement in Science

Some questions in relation to public engagement in science have also been explored during this project. These are not scientific studies, but are some activities carried out and observations made during the project. Hence they are explained here.

7.4.1 How to educate the public on a new cervical screening test?

As a part of our main study, self-sampling for HPV screening was introduced to Scotland (Dumfries and Galloway Health Board) for the first time. Introducing a new screening test was challenging, even though it was offered within the research domain. We had to educate the public carefully, on this new cervical screening test, as we never wanted to disregard the existing screening test, cervical cytology (smear) test. In fact, our aim was to bring the defaulters back to the standard cervical cytology screening programme, exploiting the benefits of self-sampling.

We used public media, a website, patient information leaflets, letters and education of health professionals for this purpose. We adhered to the principle of encouraging screening as a whole. Whilst the smear test finds the stage of the cervical HPV disease that can be treated, the HPV test finds the cause of it. We told women that if they were tested positive for HPV, then they need come for a smear test.

First, we asked one objective question using the Questionnaire 1: “Did you wish more information?” This questionnaire was filled soon after they have self-collected a sample.

Then, we asked HPV positive women when they came for a smear test, if they understood about the HPV testing and this process.

We developed a dedicated, website with over 10 pages which included multiples resources for our study. The number of website hits to www.hpvscreening.co.uk was checked on 1 November 2012. Also, we have often asked women attending at the hospital smear clinic between April and May 2012, if they had visited our website.

It would be difficult to measure outcomes of these interventions. But, surrogate markers suggest that our interventions were effective at least for women those who have responded.

Fig 7.3.1.1: Questionnaire-1 analysis

	Yes	No	No answer
Did you wish **more information**?	2	265	5

Almost all (265/272=97%) of those who filled the Questionnaire 1 (Fig 7.3.1.1) answered ‘no’ to the question: “Did you wish more information?” Only two persons answered ‘yes’.

We asked women who came for a smear test, after being tested positive for HPV, if they understood about HPV testing process. This question was asked from about 90 participants. The immediate answer was yes for most (approximately 70%) of them. About 20% didn’t come up with an instantaneous answer, suggesting that they understood some of it. About 10% would like to know about it again. However, this data is based on observation and not on formally collected data. Most of them understood screening principles much better after counselling. Some participants were very grateful for explaining things in detail to them.

Forty five out of 674 total numbers of visits were from Dumfries. Only 17 new visits were from Dumfries out of which 4 were investigators. Despite the reference to this website was made in every letter that was sent to 4146 defaulters in the region, it was visited only by a small number of people in Dumfries. The real number of defaulters who visited should be about 13. We understood this trend from the inquiries that we made at the smear clinic.

We took utmost care neither to disregard nor to discourage the current screening tool- cervical smear test. However, it was difficult to convince women who were tested negative for HPV to accept their next cervical smear test for which some of them will be called in a few months' time.

About 3 in 1000 targeted defaulters have actually accessed our study website. This indicates that the website played almost no role in influencing defaulter's decision of getting screened.

Women do not appear to be confident in accepting a new screening test. A study conducted in Cameroon to assess the feasibility of self-collected HPV test in place of the cytology screening (Berner, Hassel et al. 2013) revealed that most of the women were more comfortable and less embarrassed with the self-HPV. However, most participants thought that clinician collected samples are more reliable than self-collected samples. Whilst (125/217= 57%) felt ''moderate'' or ''high'' confidence when self-collecting a sample, virtually all (216/217=99%) felt the same for the physician sampling. Similar attitudes was observed in the UK in a Manchester based questionnaire survey (Forrest, McCaffery et al. 2004) which included 200 women of Indian, Pakistani, African-Caribbean and white British origin. Although the willingness to try to use the test was high, and women did not foresee religious or cultural barriers to self-sampling, a large proportion of women were concerned about doing the test properly. This concern was greatest in the Indian and African-Caribbean groups. It appears that these women had not had an adequate understanding cervical cancer, its prevention and also about the accuracy of self-sampling. A qualitative study involving 28 Muslim women living in north-east London (Szarewski, Cadman et al. 2009) reported that women were generally positive about cervical screening, but they were concerned about not doing the self-test correctly. Although women's willingness to try self-sampling for HPV is encouraging, worries about carrying out the procedure correctly may be counterproductive (Waller, McCaffery et al. 2006). These studies highlighted the importance of educating women in order to build confidence on self-sampling, before it is offered.

Virtually all women who self-collected (245/249= 98%) in our study answered 'no' to the question: "Did you wish more information?" Only two persons answered 'yes'. Whilst this indicates that information provided was sufficient to collect the sample, it may also be a surrogate marker of information overload. Giving the right amount of information in a form that is suitable to every individual is difficult, particularly when new, complex pieces of information

should be delivered in printed format. However, written information appears to be the most accessed mode of information.

Although 902 women were able to carry out the test alone, using simple written instructions (Waller, McCaffery et al. 2006), multiple approaches should provide a better outcome than just one way of educating the target population.

7.3.3. Improving public awareness on cervical screening

Clear understanding of the pros and cons of cervical screening is important for women to make the right decision in taking part in it. A good public education should help overcoming attitudinal barriers to cervical screening. Our main aim was to raise the public awareness of the potential benefits of cervical screening.

We have used public media, a website, patient information leaflets, letters and education of healthcare professionals for this purpose. We highlighted the importance of screening, without emphasising the 'attractiveness' of the home testing method.

We broadcast a 20 seconds radio 'advert' on cervical screening in parallel to our penultimate study (offering multiple smear options to defaulters younger than 30 years) on the most popular local radio station- Westsound. This message was broadcast 8 times a day over 2 weeks. Content of the message which was delivered by Dr Hannah Smith (Foundation Year 2 Trainee) is as follows (Fig 7.3.3.1):

Fig 7.3.3.1: Westsound radio cervical screening message (20 seconds)

Hi, I am Doctor Hannah Smith. Routine screening can prevent cervical cancers from developing. So, if you haven't had a smear test in the last 3 years, please call us on (Dumfries) 241 241 to attend one of our weekend or evening clinics at Dumfries & Galloway Royal Infirmary. Please remember, cervical screening could save your life!

The Dumfries & Galloway Health Board's did a news release on 18 June. News about our research project was published on 3 local newspapers, Reporting Scotland segment of the BBC News at ten (pm), BBC local radio and two other local radio stations. It can be found on BBC online http://www.bbc.co.uk/news/uk-scotland-south-scotland-18476882

It would be difficult to measure outcomes of the interventions. But, surrogate markers suggest that our interventions were somewhat effective. Although one-off public awareness campaign is always better than nothing, an ongoing public awareness programme should be much more effective. Dumfries and Galloway's Screening Programme Co-ordinator was surprised to see such a good response (122/1311=9% have had a smear test at 2 months) from this 'hard to reach' younger defaulters cohort. The radio 'advert' may have contributed to it.

Although a personal approach based on providing information and individual counseling appears to be successful in encouraging non-attendees to reconsider their decision and participate in the cervical screening (Campbell, MacDonald et al. 1996), this strategy may not be easily executed. Furthermore, evaluation of the effectiveness or cost-effectiveness of methods that we have used to raise the public awareness on screening remains difficult.

7.4 Recommendations

1. Sending a letter which is different to the routine recall letter when defaulters are recalled could be recommended. The content of which may be similar to the main body (without multiple options) of our letter-1 (Fig 3.3.4). Such a pilot project could be implemented without spending any extra money in a Health Board. According to the national cervical programme publication number 26 (NHSCSP 26), "Since the publication of the 1997 report, very little research evidence has been produced that specifically addresses questions related to the content cervical screening programme letters and the information needs of women receiving these materials." We believe that the evidence we developed based on the initial invitation letter (which was sent to 5256 defaulters in Dumfries & Galloway) justifies this recommendation.
2. Replication of methodology of some of our studies in another health board in Scotland as a pilot project is suggested. In our overall experience, one cycle of the 'kit' method could be recommended.
3. It appears that more effective system/s should be put in place to identify and remove women who are not eligible for screening (e.g. deceased, total hysterectomy, living abroad or another area) from the call-recall database. This will not only save resources, but also build the public confidence on screening programme, as it would ensure clean and accurate statistics.

4. Recognise self-sampling for HPV screening as a primordial screening test (a test which tells you who should be further screened), for defaulters. The lay term could be 'a pre-screening test'. This test will tell whether or not a defaulter needs to come for a smear test. About 90% of pre-screening positives will take the next (primary) screening test.
5. It may be worthwhile considering re-commencing hospital smear clinics. Frequency of the clinic could be little as once a month. This may help small proportion of defaulters to come back to screening. However, this intervenation may not significantly increase the screening coverage. A fair proportion of women attending at our hospital smear clinic verbally requested us to continue the hospital smear clinic.

7.5 Questions for future research

1. I believe that examining the feasibility of offering more flexible screening options to defaulters e.g. urine testing is really valuable. Although the sensitivity of such methods could be far from ideal, getting defaulters back to any form of screening is a positive behavioural change. Such defaulters may ultimately accept better screening tests.
2. Further research into accuracy of the SCCRS database would strengthen the findings of our study. It may be worth examining how accurate are the cervical screening databases in other areas in the UK.

7.7 CONCLUSIONS

Whilst about 6% defaulters had smears in 6 months without any intervention, about 14%-31% were screened 6 months after our interventions. Offering the option of self-sampling along with the cervical smear to defaulters may significantly increase the number of new defaulters referred to colposcopy. Practical barriers are often the cause of women not attending for cervical screening and offering more options, particularly the option of self-sampling at home, increases screening coverage.

This project has shown that by adopting a flexible approach with regards to the sensitivity of this test and the needs of women, a great deal can be achieved. We should continue to examine what is most suitable for individuals rather than sticking to a traditional method and adapt accordingly.

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Appendix 1 (GROSS DATA)

Gross data of all defaulters who requested self-sampling, in the order that they were requested

Table 8.1.1: Gross data of all 129 kit requests (1000 study) in the order that they were requested

No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
1	41	6							
2	54	never							
3	48	12							
4	35	14							
5	31	9	pos	neg	neg				
6	47	5	pos	pos	neg	neg	normal	1	
7	41	17	pos	neg	neg	neg	normal	1	
8	55	9	pos	neg	neg	neg	unsat	3	
9	55	8							
10	34	14	pos	pos	severe		hgCIN	1	CIN3
11	54	8	pos	pos	neg	neg	normal	1	
12	50	never							
13	55	9							
14	54	6			neg**				
15	31	never	pos	neg	neg	pregna			
16	53	7	pos	neg	neg				
17	55	6							
18	44	11							
19	52	10	pos	neg	neg				
20	45	5							
21	37	bnc-3*	pos	pos	bnc				
22	33	never							
23	39	9	pos	pos	neg				
24	55	6							
25	45	8	pos	neg	neg	neg	hgCIN	1	CIN2
No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
26	52	6							
27	31	never	pos	neg	neg	neg	normal	1	
28	42	5	pos	pos	neg				
29	50	5	pos	neg	neg	neg	normal	1	
30	55	8							
31	55	6							
32	44	6			neg**				
33	51	10	pos	pos	neg	moder	hgCIN	2	CIN2
34	40	4							

35	43	5	pos	neg	neg	neg	normal	1	
36	46	16							
37	35	9							
38	32	5	pos	neg	neg	neg	lgCIN	1	CIN1
39	43	24	pos	pos	neg				
41	43	7	pos	pos	neg				
41	46	5	pos	neg	neg	bnc	lgCIN	1	CIN1
42	55	5	pos	neg	neg	neg	normal	2	
43	41	8							
44	47	5							
45	44	5							
46	36	bnc-3*							
47	55	8							
48	52	5			neg**				
49	53	8							
50	44	5							
No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
51	52	13							
52	37	12							
53	53	9							
54	37	never							
55	36	8	pos		neg				
56	39	6	pos	neg	neg	neg	normal	1	
57	33	never							
58	53	4							
59	50	12							
60	33	never							
61	47	9							
62	55	unsat3*	pos	neg	unsat	neg	normal	2	
63	53	12							
64	44	9	pos	pos	severe		?invasio	2	CIN3
65	41	19							
66	40	8							
67	44	9	pos	neg	neg				
68	43	5							
69	31	5							
70	45	never	pos	neg	neg				
71	45	12							
72	44	9	pos						
73	43	5	pos	pos	neg	neg	normal	1	
74	51	5	pos	neg	neg	neg	normal	1	
75	54	6	pos	pos	neg	neg	normal	2	

No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
76	51	6							
77	45	9							
78	47	9							
79	52	6	pos	neg	neg	neg	normal	1	
80	32	9							
81	40	6							
82	50	17	pos	na	neg				
83	37	13							
84	54	8	pos	neg	unsat	neg			
85	46	5							
86	49	unsat2*							
87	49	12							
88	49	9	pos	pos	neg	neg	?lgCIN	1	cervicitis
89	52	never							
90	31	5							
91	49	9							
92	37	4							
93	50	5							
94	44	6	pos	na	neg	neg			
95	41	never							
96	55	5							
97	39	6	pos	pos	neg	neg	normal	1	
98	41	8							
99	41	12							
100	42	8							
No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
101	31	6							
102	41	9							
103	48	6							
104	49	10							
105	34	never							
106	43	13							
107	41	never							
108	31	6							
109	42	7							
110	53	7							
111	43	13	pos		neg				
112	36	5							
113	44	6			neg**				
114	52	6							

115	51	4							
116	36	5							
117	33	bnc-7*							
118	47	4							
119	54	11							
120	48	4							
No	Age	Last smear	HPV vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colp	TZ	Histology
121	52	10							
122	35	never							
123	47	17							
124	35	9	pos	na	mild				
125	54	7							
126	30	9	pos	pos	mild	bnc	lgCIN	1	CIN1
127	40	4							
128	48	5							
129	32	5							
			pos=42	pos=15	pos=5	pos=3	pos=7		pos=7

Table 8.1.2: Gross data of all 45 kit requests (200 study)

No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colpos	TZ	Histology
1	31	never							
2	39	8			unsat**				
3	37	6	pos	neg	neg				
4	38	8							
5	54	5	pos	neg	neg	neg	?lgCIN	1	cervicitis
6	38	6							
7	39	5							
8	55	5	pos	pos	neg	neg	normal	1	
9	51	12	pos	pos	neg				
10	45	6	pos	neg	neg	neg	normal	1	
11	50	10	neg						
12	41	4*	pos	na	neg				
13	41	6	pos	neg	neg	TAH 2013			normal
14	33	5	pos	na	bnc	bnc			
15	44	8							
16	52	6			neg**				
17	48	9			neg**				
18	52	5	pos	pos	neg				
19	47	13	pos	neg	neg				
20	48	7	pos	neg	neg	neg	normal	2	
21	52	9	pos	neg	neg	neg	normal	2	
22	55	9	pos	neg	neg	neg	normal	2	
23	39	never	pos	pos	neg				

24	31	never	pos	na	neg				
25	55	6							
No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 (2012)	Smear2 (2013)	Colpos	TZ	Histology
26	52	5							
27	54	6	pos	na	neg				
28	33	unsat3*	pos	na	neg	neg	normal	1	
29	46	6	pos	na	neg				
30	45	5	pos	neg	neg	neg	normal	1	
31	52	5	pos	neg	neg	neg	unsat	3	
32	39	4	pos	pos	neg	neg	normal	1	
33	52	4							
34	55	6							
35	33	unsat11*	pos						
36	43	5							
37	45	9							
38	50	17							
39	37	4*							
40	52	5							
41	40	16							
42	38	never							
43	53	4							
44	44	13	pos	pos	severe		hgCIN	1	CIN2
45	36	8*							
46	54	6	pos	na	unsat	neg			
			pos=24	pos=6	pos=2	pos=1	pos=2		pos=1

Table 8.1.3: Gross data of all 158 kit requests (2000 study)

No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histology
1	37	4	pos						
2	30	4	pos	no result	neg				
3	32	4	pos	neg	neg				
4	33	7	neg						
5	31	never	neg						
6	36	4							
7	30	5	pos	no result	neg				
8	38	6	neg						
9	52	8	pos	neg	neg	neg	normal	2	
10	37	4	neg						
11	53	11	pos						
12	45	11	neg						
13	55	22	neg						
14	33	3*	neg			bnc**	?lgCIN**	1	metapla**
15	48	never	pos	no result	neg				

16	43	4	pos	na	neg	neg			
17	41	7	neg						
18	50	8	neg						
19	42	9	neg						
20	43	6	pos	unsat	neg	neg	normal	2	
21	34	5							
22	38	6							
23	53	unsat 2*	pos	neg	neg				
24	39	4							
25	33	6							
26	41	10	pos		neg				
27	31	never	neg			neg**			
28	45	never	pos	neg	neg	neg	lgCIN	1	cervicitis
29	55	7	pos	neg	neg	neg	lgCIN	1	CIN1
30	31	4	pos	neg	neg	neg	normal	1	

No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histo
31	39	4			unsat	neg			
32	35	5	neg						
33	30	6	pos	pos	neg	neg	normal	1	
34	48	4	neg						
35	36	5	pos	na	neg				
36	35	4	neg						
37	43	22							
38	49	7	pos	neg	neg	neg	lgCIN	1	CIN1
39	33	13							
40	39	4	pos	pos	neg				
41	45	9							
42	39	4	neg						
43	54	12	neg						
44	47	bnc3*	pos	neg	neg	neg	metapla	1	
45	46	4	neg						
46	41	7	pos	neg	neg	neg	hgCIN	1	CIN2
47	54	5	pos	neg	neg	neg	normal	1	
48	48	5	neg						
49	45	7							
50	37	11	pos	neg	neg	neg	?lgCIN	1	normal
51	48	5			neg				
52	55	6	pos						
53	53	13	neg						
54	44	15	neg						
55	53	5	pos	na	neg				
56	45	never							
57	48	5							
58	45	4							
59	53	7	pos	neg	neg	neg	metapla	1	
60	40	7	pos	neg	neg	neg	?lgCIN	1	No biopsy

No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histo
61	53	12	neg						
62	33	5	neg						
63	44	5	neg						
64	53	14							
65	34	4							
66	55	7	neg						
67	47	8	neg						
68	50	9	pos	neg	neg	neg	normal	2	
69	37	12	pos						
70	37	bnc5*	pos	neg	neg				
71	53	unsat 2*	pos		imposi				(1b1)
72	38	8							
73	43	5	neg						
74	43	7	pos	neg	neg				
75	51	never	neg						
76	41	4	neg						
77	50	5							
78	34	4	neg						
79	43	4	pos	neg	neg				
80	42	10							
81	38	4	neg						
82	31	5	neg						
83	53	7							
84	54	7	neg						
85	48	17							
86	40	8	neg						
87	44	7	neg						
88	33	11							
89	55	6							
90	52	6	pos		neg	neg	unsat	3	
No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histo
91	51	6	pos	neg	bnc	neg	lgCIN	1	No biopsy
92	32	5	pos	pos	neg				
93	40	5	neg						
94	52	9	pos	unsat	neg				
95	45	12	neg						
96	45	8	pos	neg	neg	neg	normal	1	
97	32	never	neg						
98	31	8							
99	31	6							
100	43	4	pos	neg	neg	neg	normal	1	
101	39	5	pos	neg	neg	neg	hgCIN	1	CIN1
102	46	4	neg						
103	54	5							
104	35	never	neg						

105	49	7	neg						
106	42	5			neg				
107	54	9							
108	49	7	neg						
109	49	11							
110	43	4	neg						
111	38	8	neg						
112	51	8	neg						
113	37	6				neg***			
114	32	never	pos	na	neg				
115	53	9							
116	39	10	neg						
117	45	5	neg						
118	30	4	neg						
119	55	4	neg						
120	50	5							
No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histo
121	31	4	pos	na	neg				
122	52	10				neg***			
123	39	3*	neg						
124	46	8							
125	43	13	na	na		moder	hgCIN	1	CIN3
126	45	12							
127	44	12							
128	47	8	neg						
129	39	never							
130	44	never	neg						
131	44	bnc10*	neg						
132	34	12							
133	37	16							
134	40	9	neg						
135	49	5	neg			neg**			
136	40	4	neg						
137	43	9							
138	54	7	neg						
139	48	4							
140	35	6	neg						
141	43	6	pos	neg	neg				
142	54	6							
143	38	8	neg						
144	43	5				bnc***			
145	31	never							
146	38	never				neg***			
147	50	10	neg						
148	46	5	neg						
149	32	5							
150	41	7							

No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histo
151	50	4	pos	unsat	neg	imposi	unsat	3	
152	46	5							
153	41	8	pos			neg	hgCIN	1	CIN2
154	51	5							
155	55	4	pos	neg	neg				
156	53	12							
157	50	13	pos	na	neg	neg	normal	1	
158	39	6	neg						
			pos=47	pos=3/26	pos=1/41	pos1/3	pos=12/24		pos=6/9

Table 8.1.4: Gross data of all 50 kit requests (Older study)

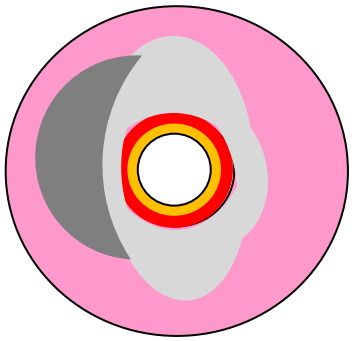
Kit group									
No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histology
1	57	4	pos	pos	neg	neg	normal	1	
2	58	8	neg						
3	59	4	pos	pos	neg	neg	normal	1	
4	56	4	neg						
5	60	14	neg						
6	57	4	pos		neg				
7	59	5	pos	pos	neg	neg	normal	2	
8	60	12	neg						
9	59	16	neg						
10	56	4	neg						
11	56	8	neg						
12	58	8	neg						
13	60	5	neg						
14	59	19	neg						
15	60	7	neg						
16	59	7	neg						
17	60	8	neg						
18	60	4	pos	unsat	neg	neg	normal	1	
19	60	4	pos	unsat	neg	neg	normal	1	
20	60	unsat5*	pos	unsat	neg	neg	normal	1	
21	60	4	pos	neg	neg				
22	60	4	neg						
23	60	unsat10*	neg						
24	57	5	neg						
25	60	4	pos	neg	neg	neg	normal	2	
26	59	6	neg						

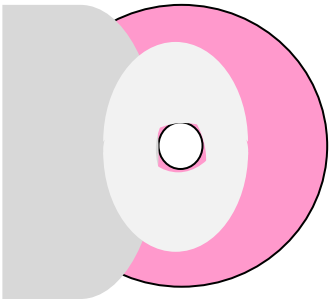
Letter group									
No	Age	Last smear	HPV Vagina	HPV of Smear1	Smear1 2012	Smear2 2013	Colpos	TZ	Histology
1	60	14	neg						
2	58	21	neg						
3	60	7	neg						
4	56	7	neg						
5	59	5	neg						
6	60	unsat2*	neg						
7	57	13	pos	neg	neg				
8	60	4	neg						
9	57	10	pos		neg	neg	unsat	3	
10	58	4			neg				
11	60	7	neg						
12	56	never							
13	57	8	pos	no result	neg	neg	hgCIN	1	CIN2
14	59	7							
15	56	4	pos	neg	neg				
16	60	7	neg						
17	58	4	pos						
18	59	11	pos	pos	neg	neg	normal	1	
19	60	4							
20	60	10	pos						
21	59	9							
22	56	6				neg**			
23	58	4	pos		neg				
24	56	never							
			pos=17	pos=4/8	pos=0	pos=0	pos=110		pos=1/1

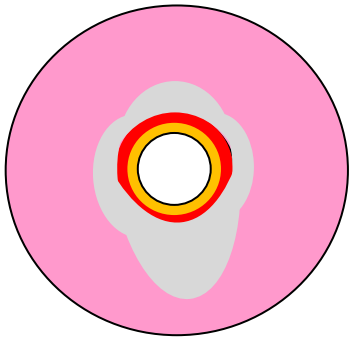
Key: Last smear= duration since the last smear test in years; HPV of Smear1= HPV result of the smear residual of the first smear test; Smear2= smear which was taken at the annual follow-up, 12 months after the first smear test; Colp= colposcopic diagnosis; TZ= type of the cervical transformation zone; bnc= borderline nuclear changes; mild= mild dyskaryosis; moder= moderate dyskaryosis; severe= severe dyskarysis; *woman on non-routine recall; **woman who had been to a smear test after having a negative smear test; ***women who had been to a smear test after being called by SCCRS in 2013; never= never had a smear test; unsat= unsatisfactory; pos= positive; neg=negative; na= not available; pregna= pregnant; ?lgCIN= suspected low grade CIN; metaplas= squamous metaplasia; TAH= total abdominal hysterectomy; ?invasio= suspected invasive cervical cancer. A woman with a negative HPV test is highlighted in green and a positive HPV test is orange. A positive smear test is highlighted in yellow and CIN is red.

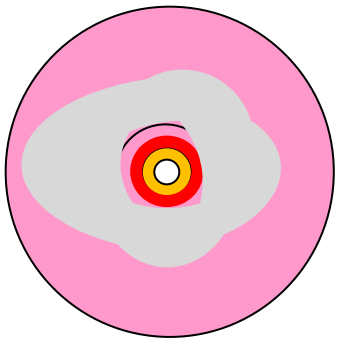
Fig 8.1.5: Screening pathway of HPV positive defaulters with abnormal colposcopic diagnosis.

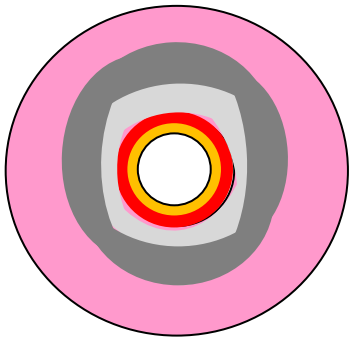
lgCIN		hgCIN		Punch biopsy site	

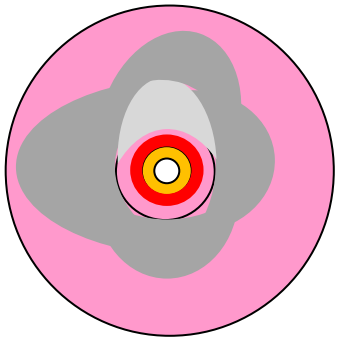
Case	Description	Year	Finding	Colpograph
1000/10	Age	(2013)	33	
	Previous treatment	No		
	Last smear	1998	Neg	
	Vaginal HPV	Apr 2012	Pos	
	Cervical HPV	June 2012	Pos	
	Smear	June 2012	Severe	
	Annual F/U smear	n/a		
	Diagnostic colposcopy	July 2012	T1TZ hgCIN	
	Histology of punch bx	No		
	Histotogy of LLETZ	July 2012	CIN3	

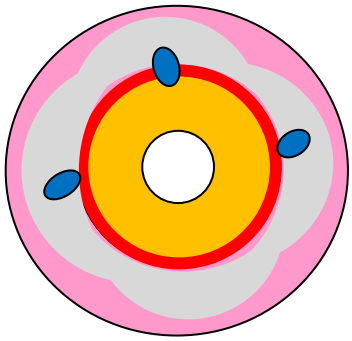
Case	Description	Year	Finding	Colpograph
1000/64	Age		45	
	Previous treatment	No		
	Last smear (non-UK)	2003	Neg	
	Vaginal HPV	Pos	Pos	
	Cervical HPV	July 2012	Pos	
	Smear	July 2012	Severe	
	Annual F/U smear	n/a		
	Diagnostic colposcopy	Oct 2012	T2TZ ?Cancer	
	Histology of punch bx	Oct 2012	CIN3	
	Histotogy of LLETZ (GA)	Nov 2012	CIN3	

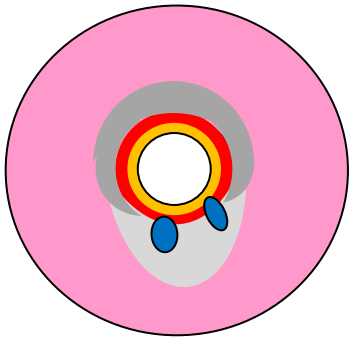
Case	Description	Year	Finding	Colpograph
200/44	Age		44	
	Previous treatment	No		
	Last smear	1999	neg	
	Vaginal HPV	Oct 2012	Pos	
	Cervical HPV	Dec 2012	Pos	
	Smear	Dec 2012	Severe	
	Annual F/U smear	n/a		
	Diagnostic colposcopy	Jan 2013	T1TZ ghCIN	
	Histology of punch bx	no		
	Histotogy of LLETZ	Jan 2013	CIN2	

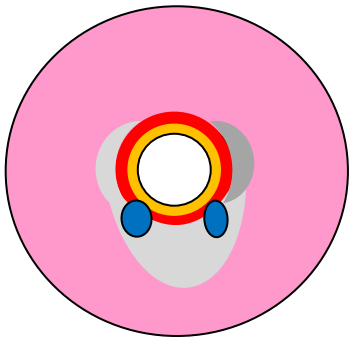
Case	Description	Year	Finding	Colpograph
2000 /153	Age		41	
	Previous treatment	No		
	Last smear	2004	neg	
	Vaginal HPV	Dec 2012	Pos	
	Cervical HPV	Not avail		
	Smear	Apr 2013	Neg	
	Annual F/U smear	n/a		
	Diagnostic colposcopy	Apr 2013	T2TZ hgCIN	
	Histology of punch bx	no		
	Histotogy of LLETZ	Apr 2013	CIN2	

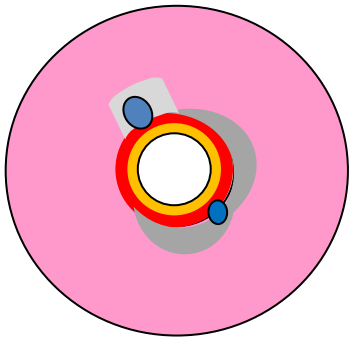
Case	Description	Year	Finding	Colpograph
2000 /125	Age		43	
	Previous treatment	No		
	Last smear	1999	neg	
	Vaginal HPV	Dec 2012	Not avail	
	Cervical HPV	Not avail		
	Smear	Aug 2013	Modera	
	Annual F/U smear	n/a		
	Diagnostic colposcopy	Sep 2013	T1TZ hgCIN	
	Histology of punch bx	no		
	Histotogy of LLETZ	Nov 2013	CIN3	

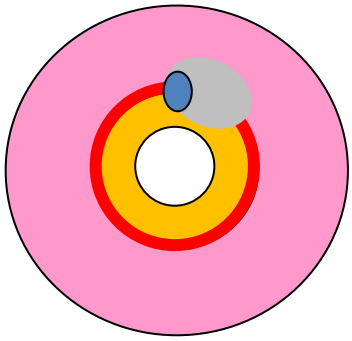
Case	Description	Year	Finding	Colpograph
1000 /33	Age	2012	51	
	Previous treatment	1995	CIN3	
	Last smear	2002	Neg	
	Vaginal HPV	May 2012	Pos	
	Cervical HPV	June 2012	Pos	
	Smear	June 2012	Neg	
	Annual F/U smear	Jun 2013	Modera	
	Diagnostic colposcopy	July 2013	T2TZ hgCIN	
	Histology of punch bx	No		
	Histotogy of LLETZ	Aug 13	CIN2	

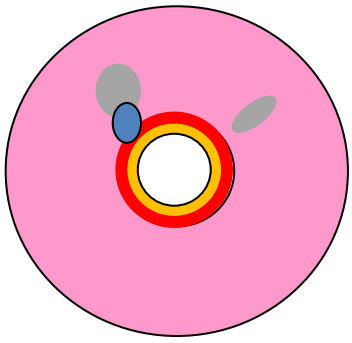
Case	Description	Year	Finding	Colpograph
2000 /101	Age		39	
	Previous treatment	No		
	Last smear	Apr 2007	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Oct 2012	Neg	
	Smear	Oct 2012	Neg	
	Annual F/U smear	Dec 2013	Neg	
	Diagnostic colposcopy	Dec 2013	T1TZ hgCIN	
	Histology of punch bx	Dec 2013	Unstis ?CIN1	
	Histotogy 2	Feb 2014	CIN1	

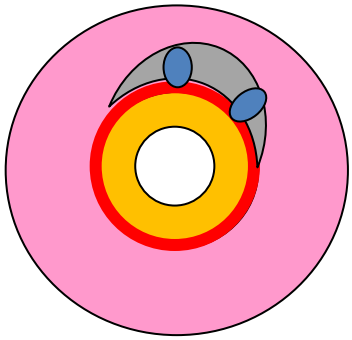
Case	Description	Year	Finding	Colpograph
Older /d17	Age	2012	57	
	Previous treatment		No	
	Last smear			
	Vaginal HPV	Dec 2012	Pos	
	Cervical HPV	Not avail		
	Smear	Feb 2013	Neg	
	Annual F/U smear	Jan 2014	Neg	
	Diagnostic colposcopy	Jan 2014	T1TZ hgCIN	
	Histology of punch bx	Dec 2013	CIN2	
	Histotogy of LLETZ			

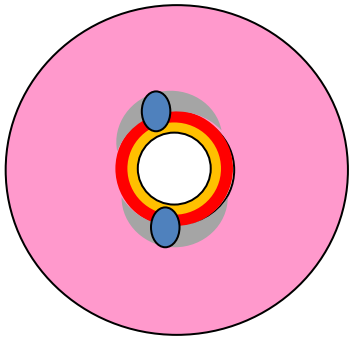
Case	Description	Year	Finding	Colpograph
2000 /46	Age		41	
	Previous treatment	no		
	Last smear	2005	Neg	
	Vaginal HPV	Oct 2012	Pos	
	Cervical HPV	Nov 2012	Pos	
	Smear	Nov 2012	Neg	
	Annual F/U smear	Dec 2013	Neg	
	Diagnostic colposcopy	Dec 2013	T1TZ hgCIN	
	Histology of punch bx	Dec 2013	CIN2	
	Histotogy of LLETZ			

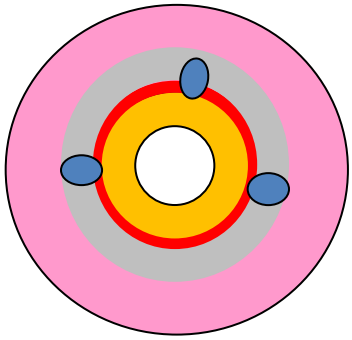
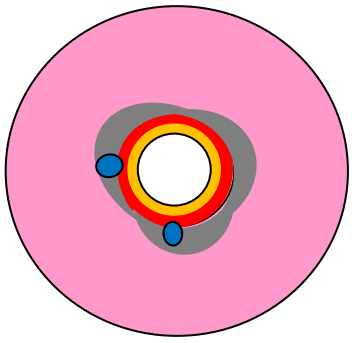
Case	Description	Year	Finding	Colpograph
1000/25	Age		45	
	Previous treatment	no		
	Last smear	2004	Neg	
	Vaginal HPV	Apr 2012	Pos	
	Cervical HPV	May 2012	Neg	
	Smear	May 2012	Neg	
	Annual F/U smear	June 2013	Neg	
	Diagnostic colposcopy	June 2013	T1TZ hgCIN	
	Histology of punch bx	June 2013	CIN2	
	Histotogy of LLETZ			

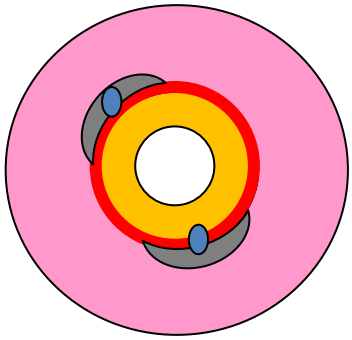
Case	Description	Year	Finding	Colpograph
1000/38	Age		32	
	Previous treatment	2004	CIN1	
	Last smear	2007	Neg	
	Vaginal HPV	Apr 2012	Pos	
	Cervical HPV	May 2012	Neg	
	Smear	May 2012	Neg	
	Annual F/U smear	June 2013	Neg	
	Diagnostic colposcopy	June 2013	T1TZ lgCIN	
	Histology of punch biopsy	June 2013	CIN1	
	Histotogy of LLETZ			

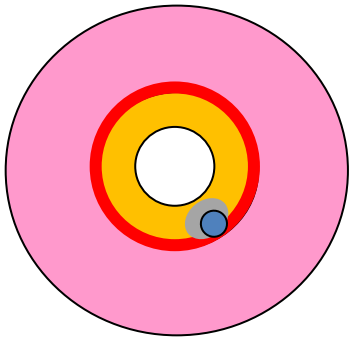
Case	Description	Year	Finding	Colpograph
1000/41	Age		46	
	Previous treatment	no		
	Last smear	2007	Neg	
	Vaginal HPV	Apr 2012	Pos	
	Cervical HPV	May 2012	Neg	
	Smear	May 2012	Neg	
	Annual F/U smear	June 2013	bnc	
	Diagnostic colposcopy	June 2013	T1TZ lgCIN	
	Histology of punch biopsy	June 2013	CIN1	
	Histotogy of LLETZ			

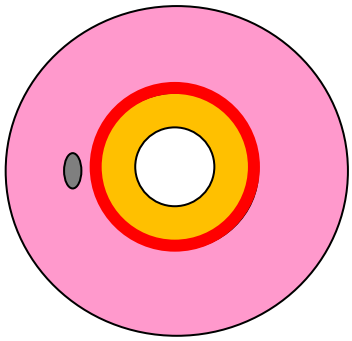
2000 /38	Age		49	
	Previous treatment	No		
	Last smear	2005	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Sep 2012	Neg	
	Smear	Sep 2012	Neg	
	Annual F/U smear	Nov 2013	Neg	
	Diagnostic colposcopy	Nov 2013	T1TZ lgCIN	
	Histology of punch biopsy	Nov 2013	CIN1	
	Histotogy of LLETZ			

Case	Description	Year	Finding	Colpograph
2000 / 29	Age		55	
	Previous treatment	No		
	Last smear	2005	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Sep 2012	Neg	
	Smear	Sep 2012	Neg	
	Annual F/U smear	Nov 2013	Neg	
	Diagnostic colposcopy	Nov 2013	T1TZ lgCIN	
	Histology of punch biopsy	Nov 2013	CIN1	
	Histotogy of LLETZ			

Case	Description	Year	Finding	Colpograph
1000 /126	Age		30	
	Previous treatment	No		
	Last smear	2003	Neg	
	Vaginal HPV	Nov 2012	Pos	
	Cervical HPV	Dec 2012	Pos	
	Smear	Dec 2012	mild	
	Annual F/U smear	Dec 2013	bnc	
	Diagnostic colposcopy	Dec 2013	T1TZ lgCIN	
	Histology of punch biopsy	Dec 2013	CIN1	
	Histotogy of LLETZ			
1000 /88	Age		49	
	Previous treatment	No		
	Last smear	2003	Neg	
	Vaginal HPV	Jul 2012	Pos	
	Cervical HPV	Aug 2012	Pos	
	Smear	Aug 2012	Neg	
	Annual F/U smear	Oct 2013	Neg	
	Diagnostic colposcopy	Oct 2013	T1TZ ?lgCIN	
	Histology of punch biopsy	June 2013	Cervicitis	

Case	Description	Year	Finding	Colpograph
200 /5	Age		54	
	Previous treatment	No		
	Last smear	2007	Neg	
	Vaginal HPV	June 2012	Pos	
	Cervical HPV	Aug 2012	Neg	
	Smear	Aug 2012	Neg	
	Annual F/U smear	Oct 2013	Neg	
	Diagnostic colposcopy	Oct 2013	T1TZ ?lgCIN	
	Histology- punch bx	Oct 2013	Cervicitis	
	Histotogy of LLETZ			

Case	Description	Year	Finding	Colpograph
2000 /60	Age		40	
	Previous treatment	No		
	Last smear	2005	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Oct 2012	Neg	
	Smear	Oct 2012	Neg	
	Annual F/U smear	Dec 2013	Neg	
	Diagnostic colposcopy	Dec 2013	T1TZ ?lgCIN/	
	Histology- punch bx	Dec 2013	Cervicitis	
	Histotogy of LLETZ			

Case	Description	Year	Finding	Colpograph
2000 /38	Age		49	
	Previous treatment	No		
	Last smear	2005	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Sep 2012	Neg	
	Smear	Sep 2012	Neg	
	Annual F/U smear	Dec 2013	Neg	
	Diagnostic colposcopy	Dec 2013	T1TZ ?lgCIN	
	Histology- punch bx	Declined		
	Histotogy of LLETZ			

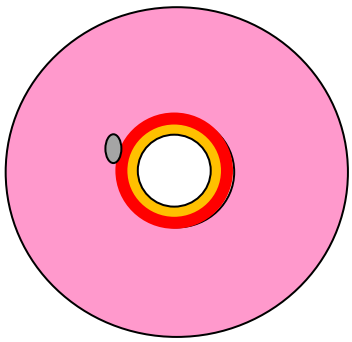
Case	Description	Year	Finding	Colpograph
2000 / 91	Age		51	
	Previous treatment	No		
	Last smear	2006	Neg	
	Vaginal HPV	Aug 2012	Pos	
	Cervical HPV	Sep 2012	Neg	
	Smear	Sep 2012	bnc	
	Smear	Mar 2013	Neg	
	Annual F/U smear	Dec 2013	Neg	
	Diagnostic colposcopy	Dec 2013	T1TZ lgCIN	
	Histology- punch bx	Declined		

Fig 8.1.6: Free comments written in the Questionnaire-1 by women after self-collecting a vaginal sample

No	Age	Comment	Cat	Co
		56-60 year old defaulter comments=11/37 (30%)		
2	57	Declined last smear invite as I work in NHS England ad for me invite would be given not 3 years as NHS Scotland. So much paper to work through may put people off participate in this study.	Ni	-
3	57	Very simple and straightforward. Only question why can I not turn the device without having to hold and click	Nc	+
5	60	I have always attended for smears, but recently the practice nurse couldn't get the smear. I went to two different nurses.	P	+
6	60	Having a very retroverted womb & tilted side wards self sampling enabled me to position the device correctly to minimise pain & discomfort – despite informing 'collectors' of a smear, this does not happen- the result being I will not have smears in the future BUT happily use this device	P	+
7	59	Due to menopause, I suffer from vaginal dryness. Reason I found it very painful to have a smear test carried out.	P	
8	59	Normal screening is very painful, the speculum used are too large. I am in pain for much of the day. This is OK.	P	+
10	59	There was a lot of paper to read, which might off putting for many!	Nc	-
11	56	It would have been better to come in a jiffy bag as mine (envelope) had got wet & torn exposing the content to my postman.	Nc	-
13	59	I have ceased to attend because it is so painful. Self sampling isn't any less painful and I don't think I have attained an adequate sample. I could insert it as instructed, but could not push the plunger sufficiently or twist it. I can still feel discomfort.	P	-
17	58	Less anxiety experienced and less painful	Nc	+
30	58	There were slight traces of blood on the brush after taking the sample.	Nc	-
		30-55 year old defaulter comments =57/235 (24%)		
39	55	I felt that this is much more comfortable than having the usual equipment inserted which always hurts and bleeds me.	Nc	+

40	42	I am distressed being called a madam- I am transgender + male. This may be the only way transmen will have smears. I was also sexually abused. Both reasons made me this very hard.	P	+
48	41	Sorry I took long to return	Nc	
50	35	Painless and easy to do. Fell less self-conscious and more relaxed at home	Nc	+
51	31	Very easy to use and much more comfortable than a smear	Nc	+
54	55	I was sore on insertion but the test was easy and once inside was OK.	Nc	
55	49	Self sampling was not uncomfortable unlike my last smear test at the doctors	P	+
63	33	Sorry I couldn't find these sheets when I sent in my sample this afternoon, I will post this in the morning 21/9/12. Hopefully you will receive them (I endorsed the green form [options list] instead)	Nc	
64	53	No mention of this (absorbent) paper until the check list before sending the sample. Perhaps a warning not to let the 'paper' sheet out of the polythene bag might be appropriate in the instruction leaflet – or somewhere due to be read BEFORE sampling!	Nc	-
67	35	The instruction say it will click every time. I turned it round 5x inside me. It didn't click.	Nc	-
74	31	I think self sampling will appeal to many, as if like me with a young family finding time and sitters to look after the children while you go (for a smear) can be difficult. Also getting appointments at your local GP surgery that fit in with your plans of free time really is difficult.	P	+
77	53	Previously cervical smear tests were very painful, this test was great- was not uncomfortable or painful.	P	+
79	52	This is the first time I have not attended my routine smear test due to various reasons – on a temporary work contract with no time off & an elderly relative requiring significant time commitment. If this self sampling works, I will certainly use it for any tests in the future.	P	+
81	32	I have made it to 32 years old without having a smear – ridiculously avoided because of embarrassment. If this self sampling was an	A	+

		option I would participate and get tested regularly.		
84	43	I find it extremely painful to have a normal smear test & this was painless, easy and quick.	P	+
86	46	Sub-total hysterectomy (one ovary and cervix remain) carried out January 2009 @ DGRI.	Nc	
94	41	Would have never got round to going for a smear. Thank you for this option.	Nc	+
95	55	No lasting after effects but didn't expect spotting.	Nc	-
96	37	I would do this every year rather than go to doctor even my doc is great!	Nc	+
102	46	The pink cap was off when I took it from the packet	Nc	-
104	45	Nice to be able to do it at home when you are free + relaxed. Thank you	Nc	+
113	55	Slightly uncomfortable, noticed small spot of blood after taking sample. No periods / have had hysterectomy in past but left with cervix.	Nc	-
116	33	Very easy and not painful in the slightest	Nc	+
124	37	I was far more relaxed before me self collect & the instructions were easy to follow. I would definitely participate in future cervical screening if I could self collect.	Nc	+
125	39	Simple and easy to do. No problems at all.	Nc	+
128	39	Going to the nurse for a smear test can be a daunting experience for some. The self test is a brilliant idea.	P	+
132	41	Used test kit four days before menstruation due to start, but some blood on test. If test invalid, I will be happy to do another test.	Nc	-
134	50	I found this method to be quick, easy and so much less painful, it is also so much more convenient than trying to arrange and appointment for screening.	P	+
135	37	Absolutely great way of doing smears, I wouldn't change anything about doing the smear this way and wouldn't hesitate to do it again.	Nc	+
151	33	Very simple to perform- I think if the test is proved to be accurate/ reliable this would be a very good option for those reluctant to cervical screening.	Nc	+

152	54	It is very convenient way. As time constrains sometimes make it difficult to attend clinic.	P	+
154	55	I have an anteverted uterus. It is unlikely that endocervical cells will be present. Even professionals have struggled to get them in the past!	P	
156	39	Needed translation	Nc	-
157	55	I do not think that access to my medical records should be necessary. I do not think I should have to take part in a study to have this option.	Nc	
164	41	I have spoken to a few women and they all agreed they would rather use this method. It is less intrusive and more chance off woman being screened. Thanks	Nc	+
167	45	I did feel some discomfort after taking the sample but it wasn't painful.	Nc	-
168	51	I've never had a screening test for any disease.	Nc	
169	54	I found this self sampling easy to do and don't have to leave the house.	Nc	+
170	55	Previously nurse has had problem due to position of cervix ?this sample adequate	P	
174	39	I had a smear test done 6 months ago, but doctor had to stop as I was in a lot of pain. I have since been sent for a scan and I am waiting on another appointment for colonoscopy.	P	
175	36	Less invasive and done at suitable time for me, no pain after self sample, smear tests always hurt! No more having to face a nurse regardless of reassurance. Best idea yet, thank you!	P	+
176	38	Less embarrassing than going to GP or clinic & also convenient as you don't have to make an appointment organise kids etc to attend. Impressed!!	Nc	+
178	31	This was easy to do, as I never had one before as I am not sexually active and I have not had sex yet.	Ni	+
183	44	I suffer from agoraphobia so it makes it difficult to get to surgery	P	
187	33	I have avoided smear tests for years as I have been suffering from a very unpleasant vaginal discharge. Too embarrassed to allow a	P	+

		Dr to perform a smear as discharge is so unpleasant so self sampling has been a good option for me. Is there a self sampling kit to test for whatever STI is causing the discharge? My ex-partner slept with a few people before I found out and ended it.		
193	42	I have always found the 'collection of cells' bit uncomfortable/ slightly painful- though the brush didn't seem as bad as last smear test. I found everything very easy, straightforward (did struggle terribly with trying to work out how to seal the bag!)	P	
200	49	Did not have an envelope in my pack to return my sample.	Nc	-
204	43	Was very easy, unlike getting it done at the doctors, never felt a thing.	Nc	+
205	51	I find this way of screening much more private and much easier for fit into your life.	Nc	+
207	54	I found this method much easier for me as I have very painful hips & this form of screening was much more comfortable.	P	+
211	47	I felt a little uncomfortable after I withdraw the Evalyn device.	Nc	-
219	55	Surprisingly easy to do. Very clear instructions. I'd definitely do this again. Thank you.	Nc	+
236	46	Never liked going for smears. This is great alternative.	At	+
438	55	Unsure if I need to have cervical screening since I have not been sexually active for over 10 years.	At	
244	33	I have never had a smear done at my GP's due to a thing that happened in my past was always unable to let it be done. This is a way I would rather tested.	P	+
245	50	So simple to use why do then not do it that way at doctors.	Nc	+
247	43	I think this is a great idea.	Nc	+

Abbreviations: Cat= category; Co=Comment (+ positive), (-negative), (blank when not clear); At= attitudinal; P= practical; Ni= (screening) is not indicated); Nc=not clear.

Fig 8.1.7: Free comments written by respondents in the options list

(a) 1000 defaulter study

	1000 defaulter study comments	Option	Category
1	"Not declined just struggle to find time, I also hate the process which delays doing something about it. Would use a smear kit test at home"	4	Pract
2	"Don't feel comfortable".	4	Atti
3	Adult living with Asperges Syndrome. Has a key worker.	6	NI
4	"don't like the uncomfortable feeling"	3	Atti
5	"FYI, due to a traumatic labour/birth resulting in a 3rd degree tare I have been panicked by the thought of a smear test, great idea to have other choices and options".	4	Atti
6	"Forgot to make appt"	1	Pract
7	Patient has had a total hysterectomy	6	NI
8	"Much more preferable! More comfortable - I always found sample at doctors rather painful."	3	NC
9	"I have not had sex for a long time also I seize up when examined it is subconscious. I do think the test home kit you sent me may be the answer but it looks bewildering but if I am in charge of carrying out this procedure then perhaps it's the best way forward".	4	Atti
10	"I am having a baby due in day! 21st June".	6	NI
11	"I am currently attending regular check-ups with a gynaecologist, surely this information must be on my notes".	6	NC
12	Patient has had hysterectomy - no dates given.	6	NI

13	"No need for the test as I have never been "sexually active" please leave me alone	6	NI
14	"I felt a little uncomfortable after I withdrew the Evalyn device"	4	NC
15	Patient living in New Zealand for past 10 years.	6	NI
16	Committed Christian (plus enclosed "10 Reasons to Believe" leaflet).	6	Atti
17	Lengthy letter received as to why she did not wish to participate.	6	NI
18	Not to be contacted again for this study. This patient has had a discussion with her GP and does NOT require screening.	6	NI
19	"As I have never had a physical relationship with anyone. So I feel that I don't need to have a "smear test".	6	NI
20	"I have had a hysterectomy 8 years ago in New Zealand (so I'm not showing that on my UK records). I have tried several times through my GP to be taken off this register but have obviously still remained on it".	6	NI
21	I find it embarrassing. If I could do it myself at home and send sample to hospital.	4	Atti
22	I do not want a test as I am not sexually active and never have been. I will get in touch with my Doctor if things change.	6	NI
23	"Kept forgetting to make an appointment. Automatically send me an appointment".	2	Pract
24	"I will make appointment with my GP… "for the 20th April"	1	NC
25	A detailed reply received with a summary of her experiences and reasons why she has defaulted to attend for smear test. (PRACTICAL)	4	Pract

26	“My experiences in the past have not been very positive and feel that I was being judged - I have a weight issue which could have been handled in a more positive way. I think the home testing is an excellent idea and one I am keen to pursue - I have never received this offer before for alternative testing although the letter states you have wrote to me in the past. Thank you for this offer.	4	Pract
27	"In January 1995 I had a radical hysterectomy for cervical cancer; everything was removed. Since then I have had 'vault' smears but do not find them very comfortable in any way".	6	NI
28	"Your records are incorrect I have had smear test at my GP practice 15/12/11"	1	NI
29	"The last smear test I had took ages, I'm overweight and have restricted movement in my hips. Usually the nurse/doctor finds it difficult. I'm embarrassed and upset".	2	Pract
30	"Not sexually active - never have been".	6	NI
31	"Quite simply been putting it off - not an acceptable excuse I know".	1	NC
32	"Daughter is severely disabled, would like to attempt urine sample test"	6	NI
33	"X assessed by Ed Psych for another matter and the test has been undertaken".	2	NC
34	"I am answering on behalf of my daughter who is handicapped and suggest that urine testing would be her best option".	6	NI
35	Patient has had a total abdominal hysterectomy in the past.	6	NI
36	"White coat syndrome". I am not trying to be difficult deliberately. Confession - did not read last letter - I would be willing to try self collection kit for HPV testing, also urine sample.	4	Pract
37	"I suffer from anxiety, depression and agraphobia. If I could do it at home".	4	Pract

38	"It's painful and most of the time they don't collect enough cells, I bleed afterwards and they said the neck of my womb had collapsed".	5	Pract
39	"Intrusive, I have never been sexually active. I am under the impression from you leaflets that means I don't have to be tested. A self collection kit would be the best option".	6	NI

(b) 200 defaulter study

	200 defaulter study comments	**option**	**category**
40	"I don't have a partner and Dr advised me it would be too painful so I feel I cannot take part in this study".	6	NI
41	Comments on phone- patient has never been sexually active - opting out of screening - patients has Down's Syndrome.	6	NI
42	Patient had a hysterectomy in 1989	6	NI
43	"Very simple to perform, I think if the test is proved to be accurate / reliable this would be a very good option for those reluctant to go to cervical screens"	4	NC
44	Please find enclosed smear test pack I am returning it as I have had a smear done at my Doctors on 30/3/2012 and the results came back clear. Thanks again'.	1	NC
45	"Less invasive and done at suitable time for me, no pain after self sample, smear tests always hurts! No more having to face a nurse regardless of reassurance, best idea yet, THANK YOU".	4	NC
46	"OPTING OUT"	6	NC
47	X has learning difficulties, Practice Nurse decided it would be too distressing and didn't carry out the test. 29/8/12	6	NI
48	"Living in England now - no further correspondence please"	6	NI
49	"I am not, and never have been, sexually active".	6	NI

(c) 2000 defaulter study

	2000 defaulter study comments	option	category
50	Participant's mother called to inform investigators that her disabled daughter is opting out of the study.	6	NI
51	"I find it very painful". Suggestions: "A smaller instrument possibly?"	6	Pract
52	"26 weeks pregnant".	6	NI
53	"Far too painful procedure".	6	Pract
54	"Had TAH & BSO 2006"	6	NI
55	"No cervix! Werthymes Hysterectomy March 2007. Cancer removed by surgery. No further treatment, 5 year follow up completed by at DGRI".	6	NI
56	"Never been sexually active so not need it please stop".	6	NI
57	"Discussed with my GP, I am not sexually active, if my circumstances change, I will have a smear",	6	NI
58	"My daughter has severe learning difficulties and would not cope with the examination".	6	NI
59	"I don't like health professionals poking about simple reason".		Atti
60	Social Services informed us that this patient has never been sexually active and hence would not attend for cervical screening.	6	NI
61	"Have had smear tests while undertaking other medical treatment privately".	6	NI
62	"Keep forgetting".	1	Pract
63	"My daughter has learning difficulties".	6	NI
64	"Have had other things on my mind".	1	Atti
65	"Not sexually active - never have been".	6	NI
66	"NB: Please see medical notes from my visit to Gynaecology Clinic a few months ago. Thanks". (has had a smear)	6	NI
67	"Don't like it".		Atti

68	"Problems with penetration mean I can't have a smear. It distresses me and I have decided not to do it. I am also sexually inactive".	6	NC
69	"Really struggle with childcare/work then no dr appointments".	4	Pract
70	"I am pregnant".	6	NI
71	"Cannot bend my leg cartridge problem. No relationships smear test is very sore and painful".	6	Pract
72	"My daughter, X is presently living in Greece and has paid privately to have a smear test carried out in January 2012".	6	NI
73	"Fear - do not wish to give any more details".		Atti
74	"Told by my previous medical practice I no longer required to be tested".	6	NI
75	"I have problems with my bones and have a lot of pain so it is very difficult". "I would be very interested if you could test with urine as this would be much more acceptable for myself".		Pract
76	"I have an annual smear test with a private gynaecologist".	6	NI
77	"I do not want a test as I have never been sexually active"	6	NI
78	"I have learning disability and do not understand the procedure and also have a fear of doctors/nurses with procedures I don't like".	6	NI
79	"Absolutely GREAT way of doing smear's, I wouldn't change anything about doing the smear this way and wouldn't hesitate to do it again".	4	NC
80	"I haven't declined the testing; I was pregnant with my 2nd child and was advised to wait until after I gave birth, I will be making an appointment with my GP ASAP now I have had my baby".	1	NI

81	"I have not yet made an app as I leave home 7-7.30am and return 6-7pm Mon-Fri. Surgeries are not open on Saturdays when I am at home. I will make an app when next on annual leave in November. Suggested GP Surgeries open on a Saturday".	1	Pract
82	My daughter, X has down syndrome and a smear test would be too much for her".	6	NI
83	Participant asked if her records could be amended to reflect the fact she had a hysterectomy approx 10 years ago.	6	NI
84	"Have had the above done at my practise"	1	NI
85	"I have had a smear test recently at the Cumberland Infirmary (in England)".	6	NI
86	"! Am not sexually active, I have discussed it with my family and support workers"	6	NI
87	"I think I don't need a smear test as I have been diagnosed with terminal cancer".	6	NI
88	"I have recently had a smear test on Monday at my GP surgery".	1	NI
89	"Never had one - too scared".	4	Atti
90	"I had a hysterectomy in June 2005 at DGRI as far I am aware my cervix was removed during surgery therefore I do need require to have a smear test".	6	NI
91	"I had just had surgery on my groin for an existing condition (Hidradenitis) and preferred not to have another procedure at this time".		Pract
92	Called to inform us that she has had a total hysterectomy.	6	NI
93	"X no longer resides in Scotland. She moved to USA a number of years ago and only visits now twice yearly". Signed by mother.	6	NI

94	X has a learning disability and does not fully understand the procedure. X is not sexually active. She will not allow invasive procedure".	6	NI
95	"I am pregnant and will arrange for a smear test after the birth"	1	NI
96	"I am now pregnant, so not due for a smear test".	6	NI
97	"I have made an informed assessment of my risk of getting cervical cancer and consider it to be significantly lower than the risk of a false positive result".	6	NI
98	"Had cervix removed years ago, was advised Test was pointless, have explained this to hospital but no one is listening to me".	6	NI
99	"I have attended my own GP practice for routine smear test but was informed that I did not require this as I have never been sexually active".	6	NI
100	This participant informed us that she has had a total abdominal hysterectomy for cervical invasive adenocarcinoma followed by radiotherapy.	6	NI
101	"I did not decline testing; I have been ill and couldn't get to the hospital to have this test done".	2	Pract
102	"X in United States of America at the moment".	6	NI
103	"Any time would be available for a test to be done".	3	NC
104	"My sister received a smear test for home as like the HPV test home kit. I would rather do this opposed to Dr or FPC".	4	NC
105	"I have had a hysterectomy (in Australia) and when I discussed smears with my GP said I don't need cervical screening".	6	NI
106	I have never been sexually active and I don't want the test.	6	NI
107	"I am very embarrassed about my body and don't feel comfortable with the nurse that was doing the test - to be able to do the smear test at home in privacy would be more acceptable".	4	Atti
108	"not sexually active"	6	NI

109	I have informed my GP that I DO NOT WANT THIS SERVICE. Please remove me from your mailing list.	6	NC
110	"X has downs-syndrome and will not let anyone touch her down below".	6	NI
111	"I am scared of people touching me".	4	Atti
112	"I am currently 23 weeks pregnant. I was advised during my last pregnancy not to undertake a smear until the baby was born. If things have changed then I am happy to undertake a smear in my current condition!"	1	NI
113	Participant's mother returned documents with note to inform us that X now lives in Perth, W. Australia	6	NI
114	"I am not sexually active and never have been I have discussed not having smear tests with past GPs and would seek an appointment should my situation change".	6	NI
115	Participant's mother phoned us to inform that she has never been sexually active and hence do not wish to attend for cervical screening.	6	NI
116	The patient's mother phoned us to inform that X is now living abroad and that her smear test is up to date.	6	NI
117	"Have never been sexually active…"	6	NI
118	"I feel it is embarrassing and there no information before or after and medical staff no need side manners or interest in the individual patients needs".	6	Atti
119	"Have moved back to Poland".	6	NI

(d) 'Older' defaulter study

	Older defaulter study comments	option	category
120	I have had a full hysterectomy.	6	NI
121	Not sexually active, 60 years.	6	NI
122	I had a hysterectomy 10 years ago at DGRI.	6	NI
123	Got the neck of the womb frozen years ago and since have been unable to get a proper smear test.	6	Pract
124	Last smear failed as too dry, vagifem caused discharge, 60 next year.	6	Pract
125	I went but it was too painful. They were going to send back for me but didn't so I don't want one. Thank you.	6	Pract
126	I do not wish to participate with the test as I have concerns regarding accessing to my medical records. I will have a smear test at my GP Practice.	6	NC
127	I have had a full hysterectomy.	6	NI
128	Not sexually active, 60 years.	6	NI
129	I have made an appointment on 28/11/2012 at my GP practice.	1	NC
130	Apologies for delay in getting the smear test.	1	NC
131	I have made appointment with nurse at GP Practice for the 20th November.	1	NC
132	Appointment has been made for 03/04/13 at Stranraer (GP).	1	NC
133	I have ignored previous invitations because I have found smears uncomfortable, so this was just the prompt I needed. I have never found smears "enjoyable"! I had to return to GP twice because she failed to get enough cells. Third time it was managed with a metal inserter thing (speculum). I did not find this experience comfortable, so it has put me off. I do appreciate that discomfort at a smear test is preferable to cervical cancer, so I acknowledge that I have been silly. Thank you for the information pack.	4	Pract

(e) 'Younger' defaulter study

	Younger defaulter study comments	option	category
134	I am currently pregnant and will arrange an appointment with my GP once baby is born	6	NI
135	I am in early pregnant and my midwife advised me to do the cervical screening test after giving birth	1	NI
136	I do not require a smear as I have never been sexually intimate with another person. When I have I shall arrange for a smear	6	NI
137	X is now living in Australia (signed by mother in law)	6	NI
138	I currently work two jobs with unpredictable and late and early shifts whilst also going to college so I don't have much time free. I also have a strong dislike of the doctors and hospitals and I get very anxious at the thought of going	6	Pract
139	At present I am living abroad in Germany and have arranged to be tested by a doctor here. Please take me off your list until further notice. Many thanks	6	NI
140	I thought we had exempted (personally unsuitable) but will check SCCRS (note written by GP, signed by father)	6	NI
141	I do not need one because as it states in the 1st question 2nd line in bold writing (Every woman with a cervix who has EVER been sexually intimate with another person should go for cervical screening)	6	NI
142	I can't have a test done at the moment as I am 37 weeks pregnant. I will make an appointment in a few months	6	NI
143	Filled in on behalf of X by her mother as X is currently in Australia	6	NI
144	I was raped and do not like to be touched, I cannot face doing this test at the moment, may be in the future but not this year	6	NI
145	I have not had intercourse yet	6	NI
146	Please remove from records as she now lives in Turkey with her husband + child. Thank you	6	NI
147	X stays in Australia	6	NI
148	X has severe learning difficulties and has a genetic condition Nicolaides Baraister Syndrome. She has never and will never have asexual relationship (signed by mother)	6	NI
149	I do not require a test at this time but will get one when I do. Thanks	6	NI
150	X no longer lives in UK. Please remove her from your records (signed by grandmother)	6	NI

151	My daughter now lives in Australia. Thank you (signed by mother)	6	NI
152	Disabled lady, wheelchair bound and mum (carer) doesn't wish X to have a c-smear. Thanks (note written by GP)	6	NI
153	I do not want a test because I never been sexually intimate with another person before and my periods are normal	6	NI
154	I am only on the pill for medical reasons and I have not been in a relationship	6	NI
155	My reason for not having a test is because I am single and have never had sexual intercourse, but wish to be reminded of the next routine screening	6	NI
156	No sexually & got the injection for cervical cancer vaccine	6	NI
157	I have never been sexually intimate with anyone therefore have been advised I don't need smear tests yet. If this information is wrong please let me know	6	NI
158	X has never been sexually intimate with anyone so was told that she didn't need a test (signed by mother)	6	NI
159	I don't want a test	6	NC
160	I am living in London & have smear tests there, I am up to date with screening (pp signed illegibly)	6	NI
161	I am currently pregnant and was advised not to be tested during pregnancy. Will gladly make appointment if this is not the case	1	NI
162	X has been travelling for the last 20 months, will be returning in the new year (signed by mother)	1	Pract
163	I have had a smear test done on Tue 23rd October at my GP	1	NI
164	I am pregnant at was told at my first booking (of pregnancy) that I will get one done 6 weeks after giving birth. I will contact my GP for this	6	NI
165	I don't believe I need the test at the moment, I could be wrong but I'd prefer not to waste anyone's time	6	NI
166	I am pregnant so not to be able to attend. I will make appointment after my baby is born	6	NI
167	I am anxious about the procedure to make an appointment, I would be more than happy to carry one at home and return it but these letters make me nervous, I feel physically ill when I see them. While I understand it is in my best interest to come. I am not ready to do so at this time	6	Atti
168	Pregnant just now baby due 18/11 arranging with clinic for post baby screening	1	NI
169	Due to health anxiety I will make an appointment with my GP when I feel able to do so	1	Atti

170	I have recently received letters asking me to go for a smear check up but as I am currently living away from home for University I cannot go for the check-up until Christmas holiday period	1	Pract
171	I will see my GP	1	NC
172	I had my last smear in Australia January 2012	1	NI
173	I've just been too busy. Now I have more time. I will go	1	Pract
174	I have an appointment on 12/11/12 at my surgery	1	NC
175	I would like a female Dr or Nurse to do the test please	2	Pract
176	Preferably after 6pm, thanks	2	NC
177	Please could I have appointment Monday night at 6pm	2	NC
178	Monday or Tuesday after 7pm	2	NC
179	I work shifts so weekends 03/11/12 or 17/11/12 would be fine. If an evening appt is made I may have to rearrange it	2	Pract
180	I am still a virgin and feel i don't need a cervical smear	2	NI
181	I am in Australia until the 14th Nov so, it would need to be after then	2	Pract
182	Preferably Tuesday between 12-1	2	NC
183	Bad experience last time and also recent problems have led to this delay emotional stress	5	Pract

Table 8.1.8: The main reason for non-attendance (reason documented in the smear clinic clerking sheet)

No	Age	HPV	Main reason stated	Other	Category
1	54	Y	'Embarrassment'	N	Atti
2	22	N	'They took my sample and told me that they can't process it, because I am no longer registered with the practice (in Dumfries & Galloway). I had to register with a GP in Edinburgh as I go to the Edinburgh University'	N	Pract
3	47	N	(No reason recorded)	-	NC
4	45	N	(No reason recorded)	-	NC
5	40	N	(No reason recorded)	-	NC
6	39	Y	'I got the first letter, to be honest. I was hoping to go after the reminder letter. I changed my address and didn't get the reminder'	N	Pract
7	48	N	'I found smears are painful all the time. The nurse struggled to take my last smear and it was really painful'	N	Pract
8	22	N	'I have never had sex'	N	NI
9	29	N	'I don't want the practise nurse to take it. I would rather get it done by a doctor, but it is not an option'	N	Pract
10	24	N	I came to Scotland recently from Poland. I never had it before'	N	Pract
11	26	N	'I had a smear in 2006. I was worried that it may pick up anything nasty'	N	Atti
12	21	N	'Didn't get round making an appointment due to various reasons- busy, anxious as I never had it'	N	Pract
13	29	N	'I am busy with my own business. I am free only on Thursdays. I tried to make an appointment, but, my practice doesn't do smears on Thursdays'	N	Pract
14	29	N	'I didn't get round making an appointment'	N	Pract
15	35	N	'I've got a little child and a toddler, husband is working full-time. I could not go for a smear in a weekday'	N	Pract
16	22	N	'Busy with my job'	N	Pract
17	24	N	'I had a smear in 2008. I busy at work. I tried to fix an appointment, but didn't work out'	N	Pract
18	22	N	'I went to my practice to get a smear test. The nurse told me that it can't be done as I was having a urine infection. My practice gives only Wednesday afternoon appointments, which I can't keep as I work in Glasgow'	N	Pract
19	25	N	I have never been sexually intimate with another	N	NI
20	29	N	Putting it off, actually for no real reason	N	Atti
21	48	N	'I am a nurse. I know what I am capable of... I don't want a nurse to take my smears. I always had it at the Well Women Clinic'	N	Pract
22	44	Y	I don't know why I was putting it off	N	Atti

23	59	N	I was due for a smear when have had chemo and radiotherapy for endometrial cancer. Oncology nurse said it may interfere with the smear result.	N	Pract
24	59	N	I didn't get round a smear because my last smear in 2004 was not pleasant	N	Pract
25	55	N	I thought I had my cervix removed at the time of hysterectomy (it was a sub-total hysterectomy)	N	Pract
26	32	Y	I don't know why I didn't go	N	Atti
27	37	Y	I had an abnormal smear in the past- I was a bit apprehensive	Y	Atti
28	41	Y	My previous bad experience put me off	N	Pract
29	57	Y	I work shifts and they are busy- I was not able to arrange an appointment	N	Pract
30	22	N	Anxious and embarrassed	N	Atti
31	26	N	I got 3 smear letters when I was pregnant, nothing since	N	Pract
32	24	N	I thought they took a smear when I was an in-patient on the Gynaecology was early in this year (it was just a swab, not a smear. Her last smear test was in 2008).	N	Pract
33	60	N	I have been living in my son's home since 2010. I might have missed my letters	N	Pract
34	31	Y	I have been moving my house when I got my last smear letter. I was busy with my life and job	N	Pract
35	26	N	Busy travelling around the world	N	Pract
36	59	Y	My last 3 smears have been painful	N	Pract
37	43	Y	I know the practice nurse well	N	Pract
38	59	Y	I have been busy at work and coming to the hospital to sort out a problem in my throat	N	Pract
39	60	Y	I've been living in Italy in last 5 years	N	Pract
40	29	N	I had the screening test in Poland in 2010	N	NI
41	60	Y	My last test in 2008 was really painful	N	Pract
42	30	Y	My mum's got a terminal cervical cancer, which put me off going for smears (crying)	Y	Atti
43	55	Y	I had painful smears in the past	N	Pract
44	57	Y	It is embarrassing	N	Atti
45	56	Y	My last smear test was a nightmare- a nurse and two doctors took it, yet they haven't got enough cells	N	Pract
46	28	N	I was due for a smear when I was pregnant	N	Pract
47	59	N	I have some memory problems	Y	Pract
48	56	Y	Disabled daughter, grandchild with hyperactive disorder, 2 jobs.... (very busy)	N	Pract
49	59	Y	I haven't got any letter in the recent past	N	Pract
50	59	Y	I had a bad experience when I had my last smear	N	Pract
51	21	N	I have not been sexually active until recently	N	NI
52	50	Y	Both pain and embarrassment	N	Atti
53	27	N	(No reason recorded)	-	NC
54	56	N	(No reason recorded)	-	NC
55	60	Y	I received the letter, but couldn't get round it	N	Pract

56	52	N	I went to my smears in the past. I had several personal problems, recently	N	Pract
57	22	N	I went for the smear test, but they couldn't do it because of the pain	N	Pract
58	43	N	I have been going up and down to Latvia	N	Pract
59	35	Y	Busy with my family and the job	N	Pract
60	54	Y	I had sex only once in my life. I went to a smear test, it was too sore	N	Pract
61	57	Y	I have been ill- stroke, heart disease and COPD	N	Pract
62	58	N	I have to go to the toilet very often as I have this diarrhoea for many years. So, I never leave my home	N	Pract
63	39	Y	Smears are uncomfortable- my last one at doctors was painful	N	Pract
64	55	Y	Busy with life- looking after disabled sister, old father, 3 children whilst working night shifts.	N	Pract
65	36	N	I have no issues with having smears. I never had any smear letter since 2008.	N	Pract
66	60	Y	I had suffered from serious emotional problems at the menopause, which put me off	Y	Pract
67	59	Y	Busy with job and life, I was not able to fix an appointment	N	Pract
68	54	Y	I find it difficult to sit down or lie down due to arthritis	N	Pract
69	43	Y	I have actually booked an appointment in 2010, but never got round	N	Pract
70	39	Y	I never had a smear letter. I am living in 44A, one of 5 studio flats. Perhaps, my address is wrong (Never been screened, the address in the SCCRS was just Studio 44)	N	Pract
71	55	Y	I would rather avoid familiar people doing my smear	Y	Pract
72	52	Y	They tried 3 times when I went for my last smear test. I have never been since	N	Pract
73	30	N	Gynaecologists removed a cyst in my ovary. I have been sore since	N	Pract
74	39	N	I was pregnant when I got the smear letter	N	Pract
75	43	N	I (personally) know the smear nurse at the practice- I wanted to avoid her	N	Pract
76	48	N	The smear that my GP took (a long time ago) was very sore. I didn't know that I could get it in other places	N	Pract
77	54	Y	Embarrassment	N	Atti
78	47	Y	I am self employed and work 14 hours a day.	N	Pract
79	49	Y	Very busy- I run businesses and follow my son's racing in weekends	N	Pract
80	44	Y	I made appointments but cancelled them. I suffer from irritable bowel	N	Pract
81	39	Y	I had some bad experiences when having the smear test	N	Pract
82	31	Y	(No reason recorded)		NC
83	47	Y	(No reason recorded)		NC

84	55	Y	(No reason recorded)		NC
85	39	Y	(No reason recorded)		NC
86	53	Y	I have been busy studying. I know... this is not the right age to study	N	Pract
87	37	N	I didn't receive any letter. I would have gone, if I did	N	Pract
88	53	N	I never received any letter since I had hysterectomy in Poland in 2005. Perhaps my cervix is not there (no cervix was found)	N	NI
89	48	Y	Embarrassment	N	Atti
90	52	N	Embarrassment	N	Atti
91	44	N	Didn't get a letter	Y	Pract
92	40	N	I work in the practice and I they all know me, so I didn't go	N	Pract
93	38	N	Busy with my job and the family	N	Pract
94	38	N	Very busy with my job, would have gone otherwise. I don't have anyone to cover me. (Weekend clinics are ideal for me)	N	Pract
95	32	N	I had an abnormal smear in the past. I was asked to go for it every 6 months, which put me off. (I thought you have to get it every 3 years. If I was explained it clearly, I would have gone)	N	Pract
96	48	N	I personally know my GP and the Practice Nurse	N	Pract
97	55	Y	My last smear test was not pleasant. The nurse was not nice. So, decided not to go again	N	Pract
98	59	N	I used to go to the Well Women Clinic for my smears. But, they had stopped doing it	N	Pract
99	37	Y	I don't like smears but, I like the self test	N	Atti
100	54	Y	My dad died in the year that I was due for a smear. Never got round making an appointment	Y	Pract
101	45	Y	Last smear was due when I was pregnant	Y	NI
102	56	Y	My smears have always been taken by (one particular Gynaecologist). I don't want others to take it	N	Pract
103	30	Y	I never got a letter	N	Pract
104	43	Y	I was busy then (when I was due)	N	Pract
105	32	Y	I have been busy at work, travelling up and down- I work in England	N	Pract
106	45	Y	I never-ever had a smear.... due to embarrassment	N	Atti
107	52	Y	I can't remember if I got any letter. I run a pub. I must have missed it due to busy life	N	Pract
108	39	Y	I have been pregnant each time I received a smear letter.... (I know you won't believe this)	N	NI
109	45	Y	I could not get round making an appointment	N	Pract
110	41	Y	Embarrassment	N	Atti
111	30	Y	I am self-employed- can't leave it- can't arrange an appointment out with normal working hours	N	Pract
112	50	Y	I am very busy with my 4 grandchildren- never got round it	N	Pract
113	53	Y	Never got around making an appointment. I was sent an appointment, I would have gone	N	Pract

114	37	Y	I didn't get a letter after 2009	N	Pract
115	55	Y	I didn't go since my periods stopped	N	Pract
116	39	Y	I was OK with my Practice Nurse at Kilmarnock. But, I don't like to my GP Centre in here	N	Pract
117	52	Y	I had a very bad smear last time- 3 people tried to take it. Sexual Health doctors eventually got it after half an hour	N	Pract
118	45	Y	My last smear result was filed in another woman's notes by mistake. This completely put me off	N	Pract
119	52	Y	I am busy- never managed to arrange an appointment (would have gone, if I was sent an appointment as you did)	N	Pract
120	53	Y	My last smear was very sore	N	Pract
121	52	Y	(no reason recorded)	-	NC
122	43	Y	I am busy at work- I have a full time career	N	Pract
123	48	N	I have arthritis of my hips- can't fully open my legs. I was in agony when they took my last smear	N	Pract
124	52	N	I used to come to the well women clinic for my smears. It's been stopped. I don't want to go to GP	Y	Pract
125	46	N	I am busy with my job- unable to arrange a convenient time	N	Pract
126	51	Y	I have been living with my daughter for a few years, since my neighbour's been bothering me. So, I didn't get any letter (we updated her address)	N	Pract
127	52	Y	I was in agony after my last smear test. I would have gone, if I knew that you've got smaller instruments	N	Pract
128	46	N	I have had a major operation in England when I was last due	N	Pract
129	51	N	They did cone biopsy 20 years ago- since then they didn't get enough cells which put me off	N	Pract
130	48	N	I got some memory problems	N	Pract
131	47	N	I have the bipolar disorder	N	Pract
132	39	N	(no reason recorded)	-	NC
133	35	N	(no reason recorded)	-	NC
134	32	N	(no reason recorded)	-	NC
135	55	N	I always had difficult smears	N	Pract
136	40	N	Last smear took 20 minutes - I will never go back to them	Y	Pract
137	35	N	Busy at work (NHS)	N	Pract
138	39	Y	I used to go to the well women clinic when I was in Edinburgh- here it is my GP who is a man	N	Pract
139	43	Y	Embarrassment		Atti
140	43	Y	I've got 3 children- one of them has autism. I can't literally leave home	Y	Pract
141	51	Y	I had treatment to my cervix. I was asked to come to colposcopy clinic for a smear. They mixed up the appointment. Although I was promised, I never got another appointment	N	Pract
142	42	Y	I went to my smears religiously, after my treatment for	N	Pract

			3 years. They (GP practice) said that they will send me an appointment, but never happened		
143	37	Y	I don't like it	N	Atti
144	50	Y	I am busy	Y	Pract
145	46	Y	I had a very bad experience last time (pain)	N	Pract
146	55	Y	I have problems with the health centre staff	N	Pract
147	32	Y	Childcare problem	Y	Pract
148	45	Y	I didn't get round it	N	Pract
149	52	Y	Smears are embarrassing	N	Atti
150	53	Y	I just could not arrange an appointment	N	Pract
151	34	Y	I don't like it	Y	Atti
152	31	Y	Didn't get round to it	N	Pract
153	43	Y	As GP is male and is not comfortable with male doing smear	Y	Pract
154	31	Y	It is embarrassing to go for smears	N	Atti
155	54	Y	I just didn't go	N	Atti

Key: HPV= HPV positive; other= was there any other reason for defaulting; Y=yes; N=no; Not indicated (screening was not indicated when she was called last time)

Fig 8.1.9: Free comments written in the Questionnaire 3– reasons why I declined testing

No	Ref No	Reasons why I declined testing	Category
1	2648	“I did not decline testing, I have been ill and couldn’t get to the hospital to have this test done”	Practical
2	2885	“I am scared, very-very scared, and would like tested for sexual health as well please”	Attitudinal
3	1643	“I find when I have had the test in the past (I realise it has been a long time) butt the test made me feel a bit scared and uncomfortable”	Attitudinal
4	2991	"I am very embarrassed about my body and don’t feel comfortable with the nurse who was doing the test"	Attitudinal
5	1880	“Never had one- too anxious and too scared, would rather not know if anything was wrong”	Attitudinal
6	034	"My daughter X is sexually disabled don’t no how I would be able to do the test".	Not indicated
7	062	“Because I have a vaginal fissure and I am not/ have not been sexually active"	Not indicated
8	065	“I am a virgin so it is not necessary for me to have the test”	Not indicated
9	502	"Never had sexual relations and unlikely in future. I am sterile with Tuners syndrome and do not menstruate"	Not indicated
10	915	“Really struggle with childcare/work then no doctors appointments	Practical
11	269	“Forgot to make an appointment”	Practical
12	212	“Don’t like the uncomfortable feeling”	Attitudinal
13	133	“I didn’t decline a test – simply took no action to have a test”	Practical*
14	597	“I found it very painful”	?Attitudinal

15	541	“I was going through very bad menopause symptoms, could not even stand the thought of anyone carrying out a test. Stress was very high, no explanation other than that mentioned”	Practical*
16	135	“Don’t feel comfortable”	Attitudinal
17	998	“Its painful and most of the time they don’t collect enough cells. I bleed afterwards and they said the neck of the womb had collapsed”	Practical
18	393	“I have not had sex for a long time also I seize up when examined. It is subconscious”	Attitudinal
19	1108	“‘White coat’ syndrome. I am not trying to be different deliberately”	Practical
20	009	“Not declined just struggled to find time. I also hate the process which delays doing something about it”	Practical
21	642	“I find it embarrassing”	Attitudinal
22	026	“I did not specifically decline, but never got round to replying. I have had a series of medical problems that need treatment so I ignored this. I have only had a smear once as I had differing advice from GPs. I found the experience painful and unpleasant”	Practical
23	512	“Bad experience with some doctors and nurses”	Practical*
24	640	“Very uncomfortable, do not have heterosexual/ penetrative intercourse. Work professionally with health staff”	Attitudinal
25	040	“Natural selection!!! May refuse treatment”	Attitudinal
26	867	“The last smear test I had taken again. I am overweight and have restricted movements in my hips. Usually the nurse/ doctor find it difficult. I am embarrassed and upset”	Practical
27	551	“Keep forgetting to make an appointment”	Practical

28	1302	“Not sexually active ” (never been sexually intimate)	Not indicated*
29	1434	“I am sorry for not returning my smear test. I put it away and forgot about it. I will send it very soon”	Practical
30	1318	“I had been for my smear recently. I found it too painful and then nurse had to stop. I don’t know if HPV testing would suit me better”	Practical
31	1319	“Reasons why I declined smear- after failed attempt at sexual health clinic”	Practical
32	932	“Personally it had been a painful experience resulting in Dr..... (Gynaecologist) & colleagues arranging it out at DGRI. I was given one option fo Practice Nurse, which resulted in her suggesting I go to a ‘drop-in’ clinic at Carigg Rd, feel uncomfortable just ‘drop in’. Not keen to do it your self-test”	Practical*
33	991	“I suffer agoraphobia”	Practical*

Key: *comments written in the second box has been complementary to categorisation; not indicated= screening is/was not indicated

Fig 8.1.10: Free comments written in the Questionnaire 3– suggestions to make it acceptable

No	Ref No	Suggestions about how the testing could be made more acceptable for me	Positive suggestion
1	2648	“I realise that the full routine smear test is the best way of finding the proper results so if I could have an appointment sent out please. I would prefer a female member of staff to do the test please”	Yes
2	2991	“To be able to do the smear test at home in privacy”	Yes
3	034	“I don’t no if I can get a urine test as she is incontinent. But I will do my best to try and get one”	Yes
4	062	"At this moment in time and the foreseeable future no testing is suitable for me. Thank you for being so interested in my health but I can arrange a smear test for myself at a more suitable time in my life"	Yes
5	502	“Discussed with GP ad agreed not necessary as low risk”	Yes
6	133	"Home test would suit me, as I have young children at home with limited childcare options. Taking children to a smear test is not appropriate- suggestions - Do 2 members of staff run a clinic ie. GP +Nurse, therefore if I had no childcare could a staff member supervise a child while the test was taken"	Yes
7	597	"I would rather use the self collection kit"	Yes
8	331	“Testing is never the problem. I remember when I get my period then forgot to book appt. Stupid I know but simple”	Yes
9	541	"What you have offered now is good. Especially when someone could be feeling the way I was at that time, (hopefully understood) I have never acted this way until menopause, fully agree with screening in any way that suits the individual, but not with familiar doctor or nurse (in small towns)"	Yes

10	393	“I do think the test home kit you sent me may be the answer but it looks bewildering but I am in charge of carrying out this procedure then perhaps its the best way forward”	Yes
11	1108	“Confession – did not read last letter – I would be willing to try self collection kit for HPV testing, also urine sample”	Yes
12	009	“Would use a smear kit test at home”	Yes
13	642	“If I could do it myself at home and send sample to hospital”	Yes
14	026	“I will happily try the test at home. I am sorry to waste people’s time and resources by not acting on this smear”	Yes
15	512	“for them to be far more gentle”	Yes
16	512	“Women’s Clinic- eg. Sandyford in Glasgow, Brooke Advisory”	Yes
17	040	“Home testing kits”	Yes
18	551	“Automatically send me an appointment”	Yes
19	1302	“I am unsure about this and feel I might like to talk to someone first”	Yes
20	932	“Appointment is preferred, so I can arrange for someone to come with me as I nearly passed out after leaving hospital last time”	Yes
21	991	“If I could do it at home”	Yes

Appendix 2 (RESEARCH TOOLS)

Fig 8.2.1: Screening invitation letter (30-60 years old) page 1

Department of Obstetrics & Gynaecology
Dumfries & Galloway Royal Infirmary
Dumfries

NHS Dumfries & Galloway

Date 23 July 2012

Dear Madam
Your cervical screening test

We are writing to you because our records show that you are not up-to-date with your cervical smear test. Cervical screening tests enable us to detect the curable pre-cancerous stage of cervical cancer.

Around 1000 women die of cervical cancer in UK each year. However, most of those who develop it have not been screened regularly. Not going for cervical screening is one of the biggest risk factors for developing cervical cancer.

Attendance for a cervical screening test is therefore advised.

We recognise that some women (for a variety of reasons) do not attend the routine smear test appointment. We have therefore designed a study to offer women various options for getting a cervical screening test.

Details of options are as follows

For a cervical smear test

1. You can arrange to see your GP or Practice Nurse or can attend the Sexual Health Clinic and ask for the standard, routine smear test.

2. If you prefer to attend the hospital for a smear test, then please tick that option on the attached sheet and return it to us so that an appointment can be made.

If you prefer not to have a smear test, please consider an alternative screening test called HPV testing. For further information, please visit **www.hpvscreening.co.uk**

For HPV testing

3. If you decide to collect a vaginal sample yourself for HPV testing but you feel you might need some advice or help on the day, then please tick that option on the attached sheet and return it to us so that an appointment can be made.

4. If you decide to collect a vaginal sample yourself at home, please read the instructions carefully before colleting the **sample**, sign the study **consent form**, complete the **questionnaire** and return **these 3** in the pre-paid envelope.

We hope that you will consider these options carefully and let us know your decision by completing the attached options list or self collect a sample and return it to us in the pre-paid envelope.

If you have any complaints about this research, please contact Clinical Governance Department Tel 01387 244220. If you wish to discuss anything further, please do not hesitate to contact us.

Thank you for your co-operation.
Yours faithfully

Dr Lilantha Wedisinghe
Specialty Registrar
01387 246246 ext 32801
Tel/text 07877196368 (24x7)
Email: lwedisinghe@nhs.net

Dr Gwen Baxter
Research Scientist
01387 241165

Dr Heather Currie
Clinical Lead
01387 246246 ext 32818

Version 6: 23/03/2012

Fig 8.2.2: Screening invitation letter (30-60 years old) page 2

Further information on cervical screening is available

NHS Scotland Cervical Screening Programme www.healthscotland.com/screening.aspx

NHS Cervical Screening Programme www.cancerscreening.nhs.uk/cervical/

NHS inform www.nhsinform.co.uk ; Tel: 0800 224488

تتوافر هذه المعلومات في صيغ أخرى بناء على الطلب وذلك من خلال الاتصال بالرقم 01387 241165

01387 241165 এই নম্বরে ফোন করে অনুরোধ করলে অন্যান্য ফরম্যাটেও এই তথ্য উপলব্ধ।

本資料亦有其他格式版本 請發打電話01387 241165 / 07877 196368 索取。

Šią informaciją, esant pageidavimui, taip pag galite gauti ir kitais formatais paskambinę telefonu 01387 241165 / 07877 196368.

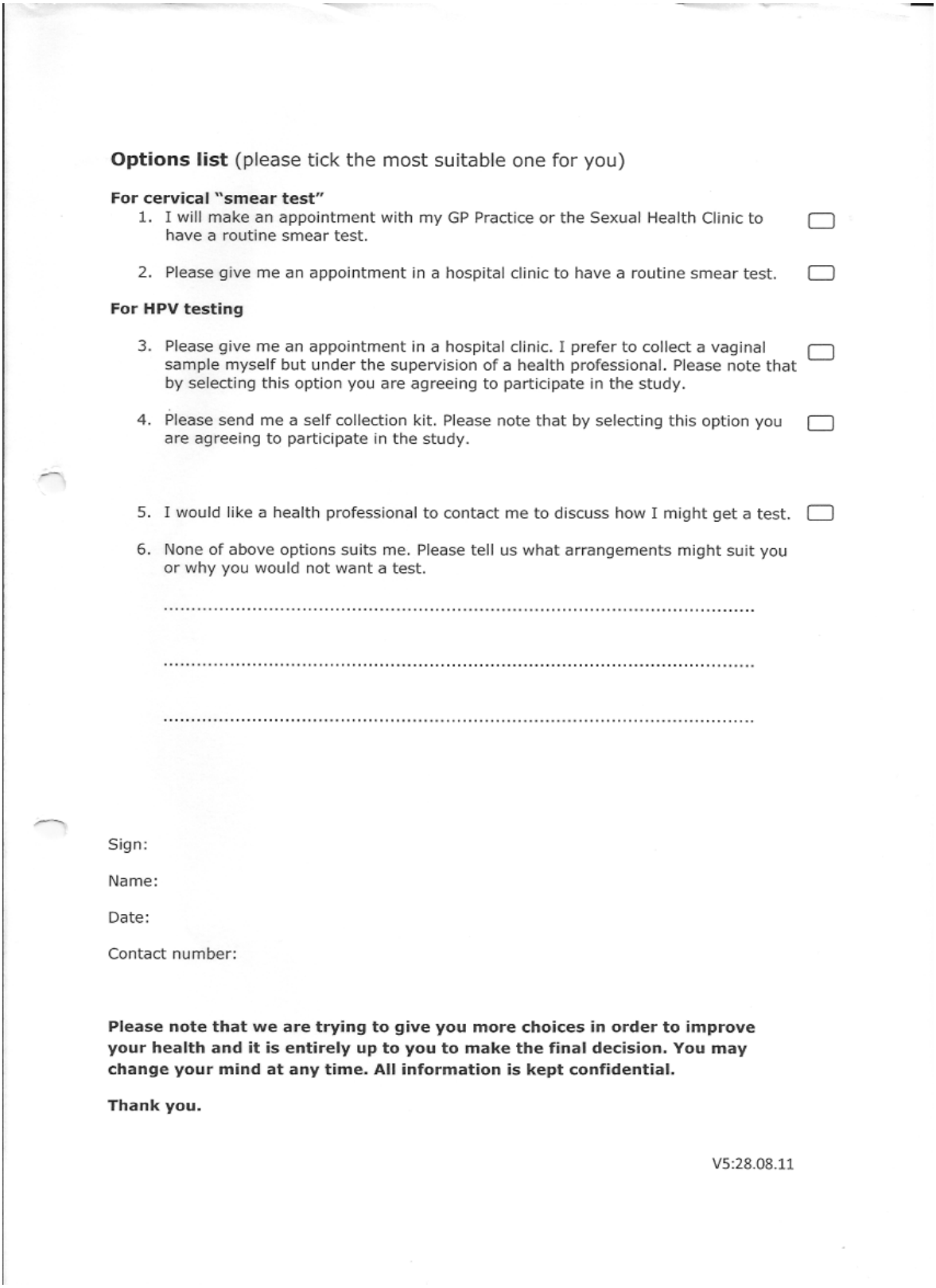
Na żądanie, niniejsza informacja jest dostępna również w innych formatach pod numerem telefonu 01387 241165 / 07877 196368.

ข้อมูลนี้มีให้คุณในรูปแบบอื่นๆอีก กรุณาโทรมาขอได้ที่หมายเลข 01387 241165 / 07877 196368

Ayrıca bu bilgiler 01387 241165 / 07877 196368 nolu telefonu arayarak diğer biçimlerde de sağlanabilir.

یہ معلومات 01387 241165 پر فون کرکے درخواست کرنے پر دیگر شکلوں میں بھی دستیاب ہیں۔

Fig 8.2.3: Options list (30-60 years)



Options list (please tick the most suitable one for you)

For cervical "smear test"

1. I will make an appointment with my GP Practice or the Sexual Health Clinic to have a routine smear test. ☐
2. Please give me an appointment in a hospital clinic to have a routine smear test. ☐

For HPV testing

3. Please give me an appointment in a hospital clinic. I prefer to collect a vaginal sample myself but under the supervision of a health professional. Please note that by selecting this option you are agreeing to participate in the study. ☐
4. Please send me a self collection kit. Please note that by selecting this option you are agreeing to participate in the study. ☐
5. I would like a health professional to contact me to discuss how I might get a test. ☐
6. None of above options suits me. Please tell us what arrangements might suit you or why you would not want a test.

.....

.....

.....

Sign:

Name:

Date:

Contact number:

Please note that we are trying to give you more choices in order to improve your health and it is entirely up to you to make the final decision. You may change your mind at any time. All information is kept confidential.

Thank you.

V5:28.08.11

Fig 8.2.4: Screening invitation letter (20-29 years old) page 1

NHS
Dumfries
& Galloway

22 October 2012

Dear Madam

Your cervical screening test

We are writing to you because our records show that you are not up-to-date with your cervical smear test. Cervical screening tests enable us to detect the curable pre-cancerous stage of cervical cancer.

Around 1000 women die of cervical cancer in UK each year. However, most of those who develop it have not been screened regularly. Not going for cervical screening is one of the biggest risk factors for developing cervical cancer.

Attendance for a cervical screening test is therefore advised.

We recognise that some women (for a variety of reasons) do not attend the routine smear test appointment. We have therefore designed a study to offer women various options for getting a cervical screening test.

Details of options are as follows

1. You can arrange to see your GP or Practice Nurse or can attend the Sexual Health Clinic and ask for a routine smear test.

2. If you prefer to attend the hospital for a smear test, then please select the clinic which suits you best on the attached sheet and return it to us so that an appointment can be made.

Alternatively, please text **07799 666 909** or email **dg.smear@nhs.net** your name, date of birth and your preferred option e.g. (Amy Smith 030186 opt2 Tues). We will facilitate your choice, confidentially.

We hope that you will consider these options carefully and let us know your decision.

Thank you for your co-operation.

Kind regards
Yours faithfully

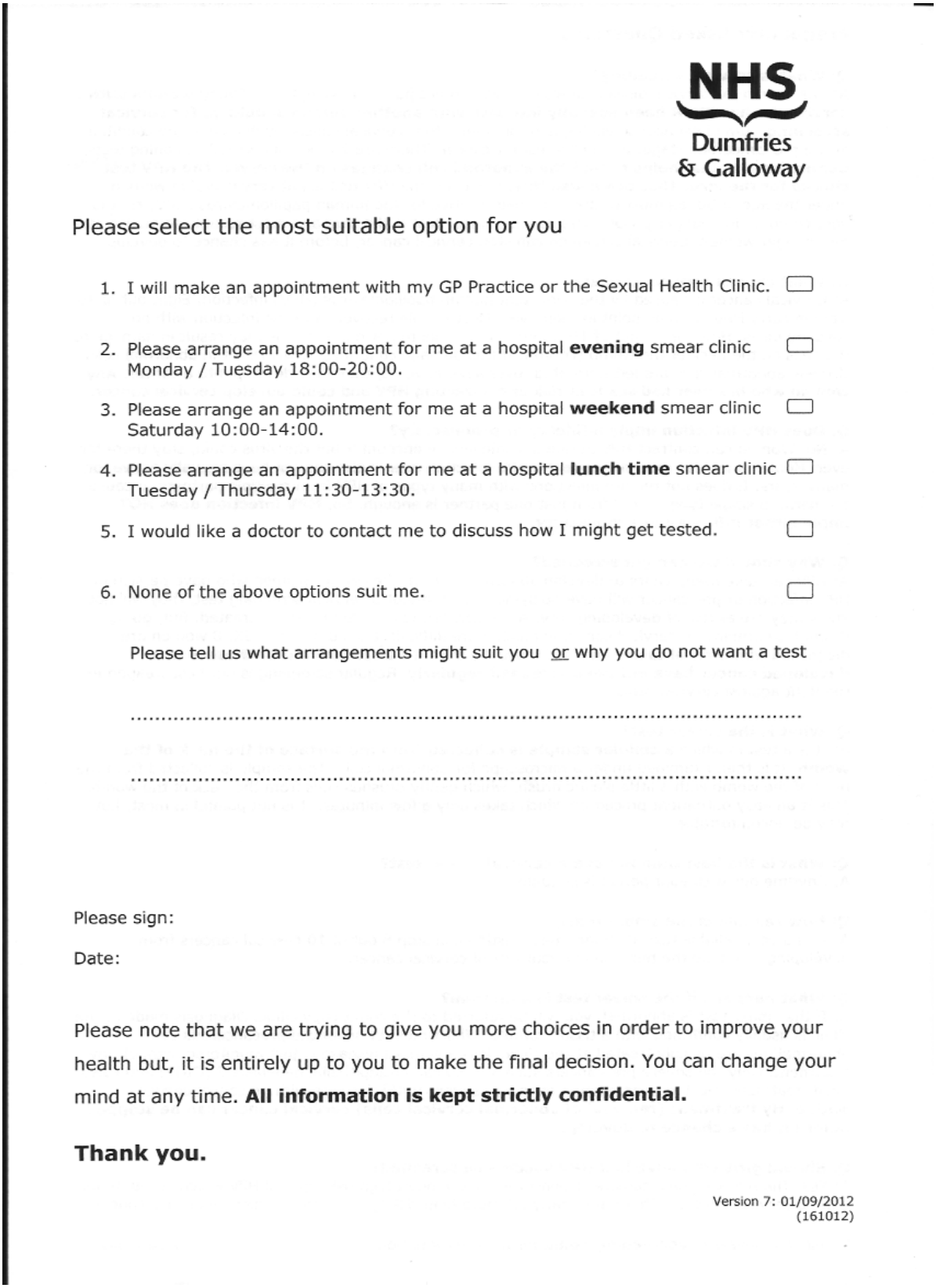
Dr Lilantha Wedisinghe
Specialty Registrar
01387 246246 Ext 32801
Tel/text 07877 196368 (24x7)
Email: lwedisinghe@nhs.net

Dr Heather Currie
Clinical Lead
Women's Health

Ms Aileen Primrose
Screening Services Manager

Version 7: 01/09/2012

Fig 8.2.5: Options list (20-29 years)



NHS
Dumfries
& Galloway

Please select the most suitable option for you

1. I will make an appointment with my GP Practice or the Sexual Health Clinic. ☐
2. Please arrange an appointment for me at a hospital **evening** smear clinic Monday / Tuesday 18:00-20:00. ☐
3. Please arrange an appointment for me at a hospital **weekend** smear clinic Saturday 10:00-14:00. ☐
4. Please arrange an appointment for me at a hospital **lunch time** smear clinic Tuesday / Thursday 11:30-13:30. ☐
5. I would like a doctor to contact me to discuss how I might get tested. ☐
6. None of the above options suit me. ☐

Please tell us what arrangements might suit you or why you do not want a test

.....

.....

Please sign:

Date:

Please note that we are trying to give you more choices in order to improve your health but, it is entirely up to you to make the final decision. You can change your mind at any time. **All information is kept strictly confidential.**

Thank you.

Version 7: 01/09/2012
(161012)

Fig 8.2.6: Participant consent form

Contacts
Dr Lilantha Wedisinghe, Specialty Registrar, Tel: 01387 246246 ext 32801 or 07877196368 (24x7) email: lwedisinghe@nhs.net
Dr Gwen Baxter , Research Scientist, 01387 241165
Dr Heather Currie, Clinical Lead, 01387 246246 ext 32818

NHS Dumfries & Galloway

Participant Consent Form

Research title: -
A research study to determine if women's health can be improved by offering more options for cervical screening.

Investigators: - Dr Currie, Dr Wedisinghe, Dr Baxter, Dr McCulloch, Dr Khalifa, Mr Wilson, Dr Breen, Professor Sasieni.

(please initial the boxes)

I _____, (Name of participant)

1. Confirm that I have read and understand the information leaflet version 5 dated 28th August 2011 for the above named study and have had opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at anytime, without giving any reason and without my medical care or legal rights being affected. ☐
3. I understand that if I withdraw from this agreement that my data and tissue will not be used for research purposes. ☐
4. I agree to my sample being tested for HPV ☐
5. I understand that my personal details will not be made public or used for reports. ☐
6. I agree to members of the research team and regulatory bodies having access to my medical records with regards to this research ☐

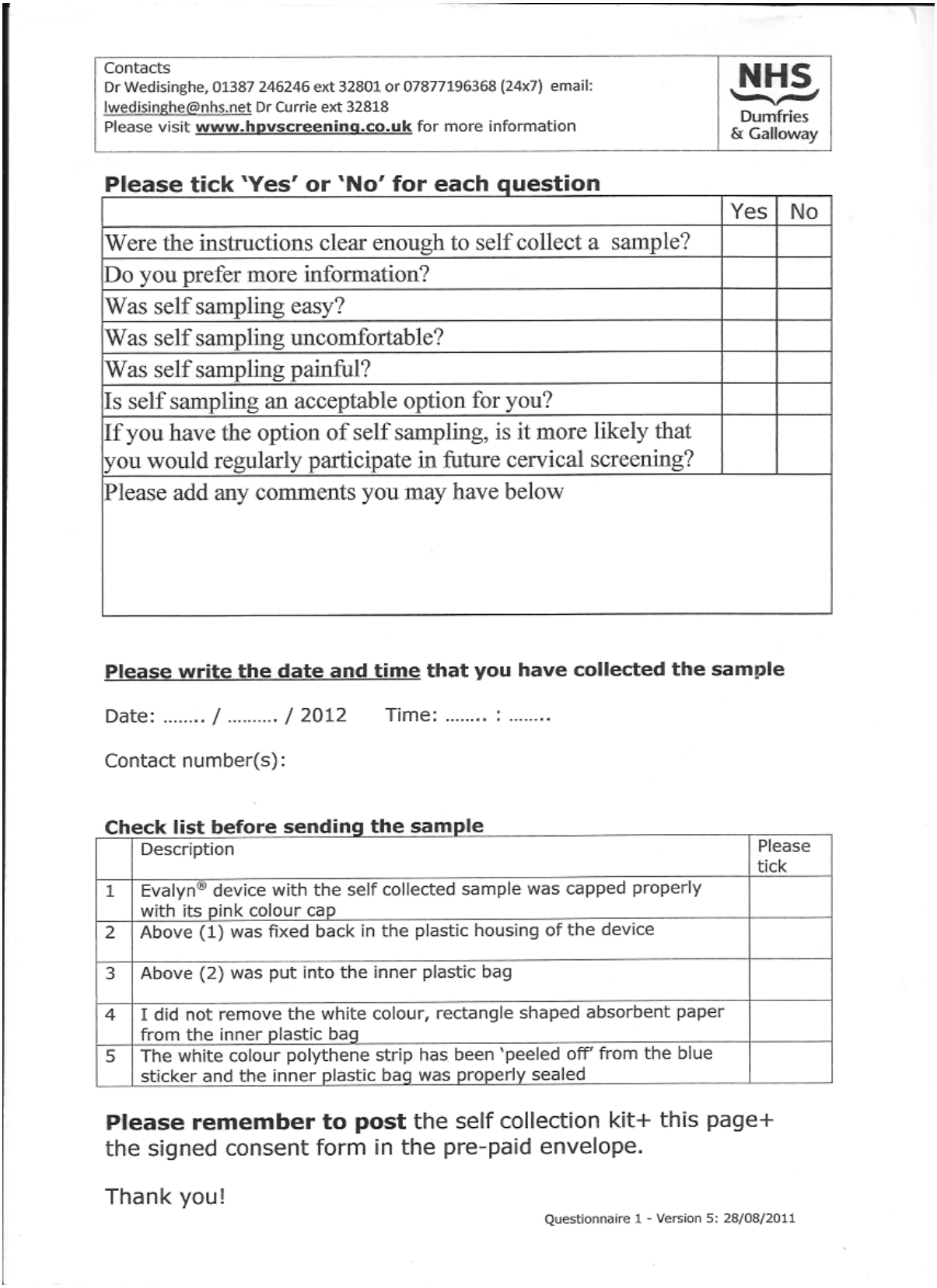
Signed _____ Date _____

Witness _____ Date _____

Ideally, this form should also be signed by a witness, but it is not compulsory.

Version 5: 28/08/2011

Fig 8.2.7: Questionnaire 1 (with the check list)



Contacts
Dr Wedisinghe, 01387 246246 ext 32801 or 07877196368 (24x7) email: lwedisinghe@nhs.net Dr Currie ext 32818
Please visit **www.hpvscreening.co.uk** for more information

NHS Dumfries & Galloway

Please tick 'Yes' or 'No' for each question

	Yes	No
Were the instructions clear enough to self collect a sample?		
Do you prefer more information?		
Was self sampling easy?		
Was self sampling uncomfortable?		
Was self sampling painful?		
Is self sampling an acceptable option for you?		
If you have the option of self sampling, is it more likely that you would regularly participate in future cervical screening?		
Please add any comments you may have below		

Please write the date and time that you have collected the sample

Date: ..... / ..... / 2012 Time: ..... : .....

Contact number(s):

Check list before sending the sample

	Description	Please tick
1	Evalyn® device with the self collected sample was capped properly with its pink colour cap	
2	Above (1) was fixed back in the plastic housing of the device	
3	Above (2) was put into the inner plastic bag	
4	I did not remove the white colour, rectangle shaped absorbent paper from the inner plastic bag	
5	The white colour polythene strip has been 'peeled off' from the blue sticker and the inner plastic bag was properly sealed	

Please remember to post the self collection kit+ this page+ the signed consent form in the pre-paid envelope.

Thank you!

Questionnaire 1 - Version 5: 28/08/2011

Fig 8.2.8: Questionnaire 2

Please tick ‘Yes’ or ‘No’ for each statement

Statement	**Yes**	**No**
Smear tests are embarrassing		
I intend to go when I am due, but I don’t always get round to it straight away		
I worry that a smear test will be painful		
I’m scared of what a smear test might find		
I’ve had a bad experience of a smear test in the past		
It is difficult to get an appointment to fit in with work/childcare commitment		
I don’t feel at risk of cervical cancer		
I’m not sexually active so I don’t need to go for a smear test		
I do not trust the smear test		
I do not need a test if I do not have any symptoms		
If you had the option of self-sampling, is it more likely that you would regularly participate in future cervical screening?		
I have never had a smear test		
My last smear was …. years ago		
Please write any other reason/comments you may have, below		

Thank you for completing this questionnaire. Please put in the box provided.

Fig 8.2.9: Questionnaire 3

Dear Madam
We understand that you are not up to date with cervical screening and have declined our offer of different ways to get either a smear test or a HPV test.

We are keen to find out what would encourage you to take up a screening test and kindly ask you to record below why you declined testing and any suggestions on how we could make the testing more acceptable for you.

Reasons why I declined the testing.
.....
.....
.....

Suggestions about how the testing could be made more acceptable for me.
.....
.....
.....
.....
.....

If you could be tested using a sample of urine would you accept that offer? Please answer yes or no

YES ☐ NO ☐

Thank you for completing this questionnaire.

We have enclosed another copy of the options should you now choose to be tested.

Please return your response(s) in the enclosed pre-paid envelope.

Fig 8.2.10: Participant information leaflet sent to women who opted for self-sampling

Frequently Asked Questions

Q: What is cervical screening?
A: The search for cervical disease in women who do not have any symptoms. **Every woman with a cervix who has EVER been sexually intimate with another person should go for cervical screening,** even if she has not been sexually active or has been in a stable relationship, for many years. Aim of cervical screening is to prevent cervical cancer by detecting the condition at the pre-cancerous stage. It is not a test for cancer. There are 2 types of cervical screening tests. **Cervical smear test helps to find the abnormal cell changes on the cervix. The HPV test checks for the virus that can cause this.** HPV test is as good as the smear test in preventing cervical cancer, and hence, it has now been incorporated into the NHS Cervical Screening Programme. Cervical screening can stop cervical cancer, before it has chance to develop.

Q: What causes cervical cancer?
A: Cervical cancer is caused by the persistent HPV infection. Eight out of 10 women carry HPV at some point in their lives. Most people recover from the infection with no consequences. However, 1 in 10 women are unable to get rid of it. Persistent HPV infection can damage the genes of the cells on the neck of the womb (cervix). Irreversible damage will result in abnormal cells. If these abnormal cells are left untreated, over several years, they may develop into a cancer. So, **any woman who has EVER had sex is at risk of contracting HPV and could develop cervical cancer.**

Q: Does HPV infection imply infidelity or promiscuity?
A: No. Women can contract HPV during a single sexual encounter, but the virus could stay there forever, if your immune system is unable to clear it. Hence, a woman may still have the HPV infection even if she has not been sexually active for many years or decades. It does not require infections with many types of HPV from multiple partners to cause the harm, a single type of HPV from just one partner is enough. So, **HPV infection does NOT imply either infidelity or promiscuity.**

Q: Why should women get screened?
A: HPV can take many years to develop abnormal cells on the cervix. Women who have persistent HPV infection or pre-cancer will have no symptoms. Without a cervical screening test, they will not know they are at risk of developing cervical cancer. Pre-cancer can be easily treated. But, going through treatment for cervical cancer is much more difficult. Each day in the UK, 8 women are diagnosed with cervical cancer and 3 of those die from the disease, **6 out of those 8 who developed cancer have not been screened regularly**. Regular screening is our best weapon in the fight against cervical cancer.

Q: What is the smear test?
A: It is a test in which **a cellular sample is collected from the surface of the neck of the womb.** It is then examined under a microscope for abnormal cells.

The sample is collected from the neck of the womb with a little plastic brush, which gently brushes cells from the neck of the womb. This is an easy outpatient procedure which takes only a few minutes. It is not painful in most, but may be uncomfortable.

Q: What is the best time to have a cervical smear test?
A: Anytime out-with your period is suitable.

Q: How reliable is the smear test?
A: It is a very reliable test. Regular smear testing can stop 8 out of 10 cervical cancers from developing. So, take the test and cut your risk of cervical cancer.

Q: What is the HPV test?
A: The HPV test is a **molecular test that detects the genetic material (DNA) of the HPV virus**. Molecular tests are generally very sensitive and accurate. For example, a self collected vaginal swab or a sample of urine is now used for Chlamydia testing rather than specimen collected from the cervical canal by a clinician. More than 10 well-known HPV tests are currently available. The HPV test requires only a few HPV infected cells to detect the virus, whereas the smear test requires at least 10,000 cervical cells. HPV can be tested in urine as well as vaginal samples.

Q: How reliable is the HPV test?
A: It is a very reliable test. HPV test, when negative, almost certainly rule out any serious disease of the cervix. HPV self testing based screening could stop 8 out of 10 cervical cancers from developing.

Q: How do I know if I collected a sufficient sample for the HPV test?
A: If you follow the instruction for self-collection given in the leaflet provided, it is extremely unlikely that your sample will be insufficient for testing. Fewer than 1 in 100 self-collected samples may not contain an adequate specimen for the test. However, the HPV test has an internal control which is clever enough to pick up such samples. Without an adequate sample, it won't give us any result. So, please don't worry, just follow the simple, self-collection steps provided in the leaflet.

Q: Where will my sample be tested for HPV?
A: Your sample will be tested at the National HPV Reference Centre Laboratory in Edinburgh. There is a well-established quality assurance system in place for HPV testing. We write to you with your HPV test result in 3-6 weeks with necessary advice.

Q: What happens if I get tested negative for HPV?
A: **A negative HPV test is more reassuring than a single negative smear test.** Theoretically, you will not get the disease without its cause. However, no screening test is 100% accurate. A mild infection could be missed. Moreover, there is a theoretical possibility that the woman might be exposed to a new *human papillomavirus*, in the due course. Hence, attending regular cervical screening is the best means of reducing the risk of cervical cancer - if you are tested repetitively and have negative results, you are much less likely to develop cervical cancer. However, having one test is better than doing nothing.

Q: What happens if the HPV test is positive?
A: **You will need a smear test.** Since treatment is available only for HPV affected cells, but not for the virus itself such as anti-viral therapy, the most pragmatic second line test available is the routine cervical smear test. Aim will be to search for abnormal cervical cells, which can be treated. However, not all HPV positive women will have an abnormal smear test as this might be a transient or mild (sub clinical) HPV infection. Cervical cells will remain normal until HPV causes irreversible damage to their genes (it is not possible to say how long it takes). Moreover, HPV can infect any part of the female lower genital tract, not just the cervix. Hence, your cervical smear test could still be normal, which is good.

Q: What happens if the smear test is abnormal?
A: If the smear test is abnormal, you will be referred to the colposcopy clinic. Diagnosis made at the clinic is usually confirmed with a tissue sample. Whilst most of advanced precancerous cell abnormalities are usually treated at the clinic, less advanced disease is just monitored without any treatment. Only the severe pre-cancers, such as cervical intraepithelial neoplasia 2 (CIN2) and CIN3 need treatment. Most women recover from less severe HPV infections with no consequences. **With early treatment (removal of abnormal cervical cells) cervical cancer can be stopped before it has a chance to develop.**

Q: Should girls who have had HPV vaccine be screened?
A: Yes. The HPV vaccine is targeted against the 2 commonest high risk types of HPV which accounts for 7 in 10 cervical cancers. There are nearly 13 more high risk types of HPV, which can cause cancer.

Q: What is the best time to self collect a vaginal sample?
A: **Anytime out-with your period** is suitable. However, you should avoid douching (washing inside the vagina), using vaginal medicines, lubricants, spermicides or tampons within the 2 days before self-collecting a sample.

Q: Is self-collection with the Evalyn® device painful?
A: No. Almost all Evalyn brush users in Dumfries & Galloway said that it was not even uncomfortable

Q: Is self-collection with the Evalyn® device safe?
A: Yes. It is a user-friendly, simple, quality tested device. Evalyn® is a sterile device, so carries no risk of infection. It is made of latex-free, high-quality plastic.

Q: Can my partner, family member, carer or friend assist me collecting a vaginal sample?
A: Yes. Please read the basic steps in the leaflet and follow them to prevent contamination.

Please visit the study website **www.hpvscreening.co.uk** for more information.

(Version 6:27/10/2012)

Fig 8.2.11: Participant information leaflet sent to younger (20-29 years) defaulters along with the multiple smear options letter.

Frequently Asked Questions

Q: What is cervical screening?
A: The search for cervical disease in women who do not have any symptoms. **Every woman with a cervix who has EVER been sexually intimate with another person should go for cervical screening**. Aim of cervical screening is to prevent (stop) cervical cancer by detecting the condition at the pre-cancerous stage. It is not a test for cancer. There are 2 types of cervical screening tests. **Cervical smear test helps to find the abnormal cell changes on the cervix. The HPV test checks for the virus that can cause this.** However, the HPV test is not very useful in women under the age of 30, as most of them will test positive for the human papillomavirus (HPV) as it is very common in younger people. The cervical smear test is the best and most reliable screening test for younger women. Cervical screening can stop cervical cancer, before it has chance to develop.

Q: What causes cervical cancer?
A: Cervical cancer is caused by the persistent HPV infection. Eight out of 10 women carry HPV at some point in their lives. Most people recover from the infection with no consequences. However, 1 out of 10 women are unable to get rid of it. Persistent HPV infection can damage the genes of the cells on the neck of the womb (cervix). This may result in abnormal cells. If these abnormal cells are left untreated, over several years, they may develop into a cancer. So, **any woman who has EVER had sex (even once) is at risk of contracting HPV and could develop cervical cancer.**

Q: Does HPV infection imply infidelity or promiscuity?
A: No. Women can contract HPV during a single sexual encounter, but the virus could stay there for ever, if your immune system is unable to clear it. Hence, a woman may still have the HPV infection even if she has not been sexually active for many years. It does not require infections with many types of HPV from multiple partners to cause the harm, a single type of HPV from just one partner is enough. So, **HPV infection does NOT imply either infidelity or promiscuity.**

Q: Why should women get screened?
A: HPV can take many years to develop abnormal cells on the cervix. Women who have persistent HPV infection or pre-cancer will have no symptoms. Without a cervical screening test, they will not know they are at risk of developing cervical cancer. Pre-cancer can be easily treated. But, going through treatment for cervical cancer is much more difficult. Each day in the UK, 8 women are diagnosed with cervical cancer and 3 of those die from the disease, **6 out of those 8 who developed cancer have not been screened regularly**. Regular screening is our best weapon in the fight against cervical cancer.

Q: What is the smear test?
A: It is a test in which **a cellular sample is collected from the surface of the neck of the womb.** It is then examined under a microscope for abnormal cells. The sample is collected from the neck of the womb with a little plastic brush, which gently brushes cells from the neck of the womb. This is an easy outpatient

procedure which takes only a few minutes. It is not painful in most, but may be uncomfortable.

Q: What is the best time to have a cervical smear test?
A: Anytime out-with your period is suitable.

Q: How reliable is the smear test?
A: It is a very reliable test. Regular smear testing can stop 8 out of 10 cervical cancers from developing. So, take the test and cut your risk of cervical cancer.

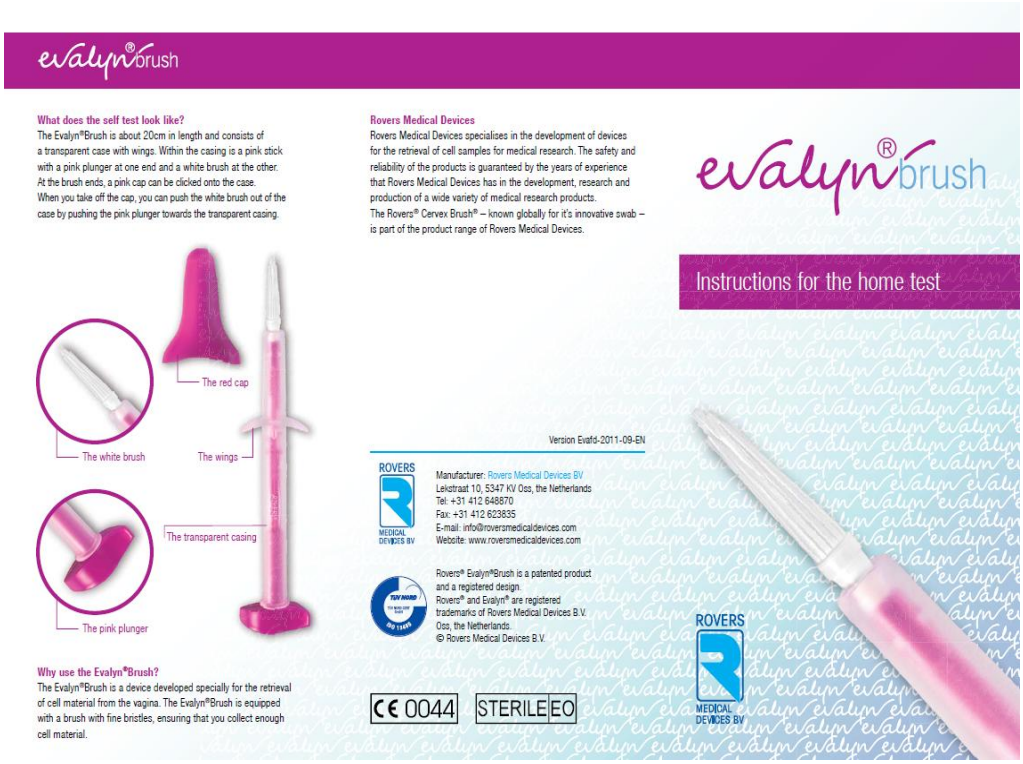
Q: What happens if the smear test is abnormal?
A: If the smear test is abnormal, you will be referred to the colposcopy clinic. Diagnosis made at the clinic is usually confirmed with a tissue sample. Whilst most of advanced precancerous cell abnormalities are usually treated at the clinic, less advanced disease is just monitored without any treatment. Only the severe pre-cancers, such as cervical intraepithelial neoplasia 2 (CIN2) and CIN3 need treatment. Most women recover from less severe HPV infections with no consequences. **With early treatment (removal of abnormal cervical cells) cervical cancer can be stopped before it has a chance to develop.**

Q: Should girls who have had HPV vaccine be screened?
A: Yes. The HPV vaccine is targeted against the 2 commonest high risk types of HPV which accounts for 7 in 10 cervical cancers. There are nearly 13 more high risk types of HPV, which can cause cancer.

Please visit **www.hpvscreening.co.uk** for more information.

(Version 7: 01/09/12)

Fig 8.2.12: Evalyn brush information leaflet (page 1)



Evalyn brush information leaflet (page 2)

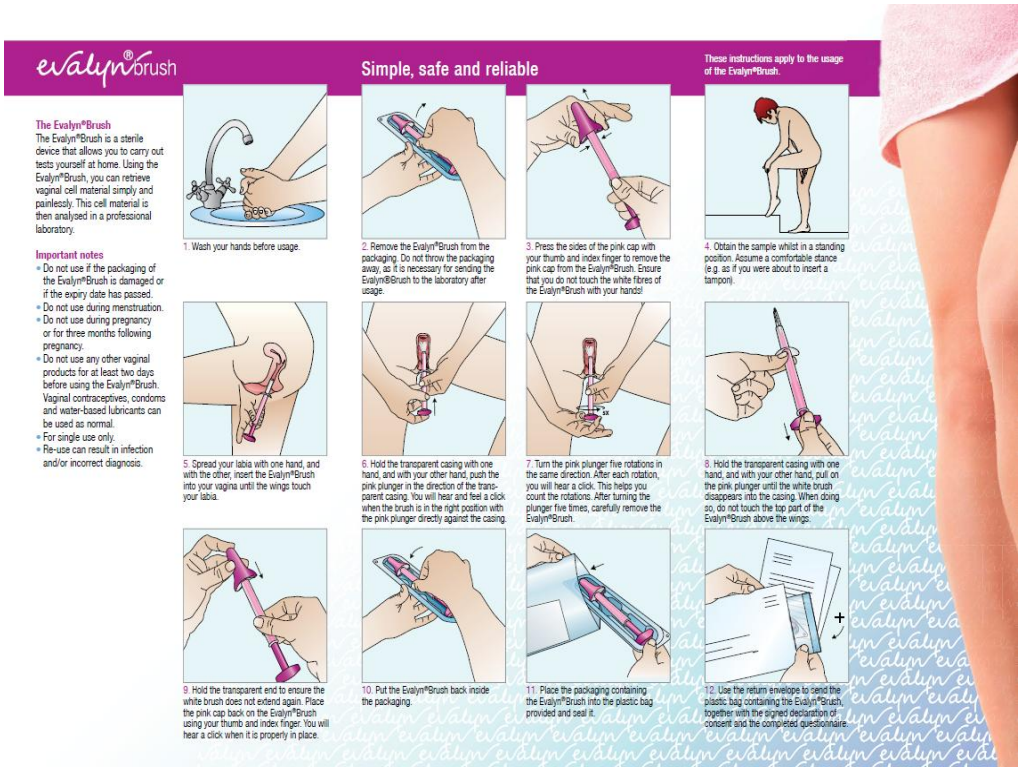


Fig 8.2.13: Evalyn brush self sampling kit inside its pre-paid return envelope

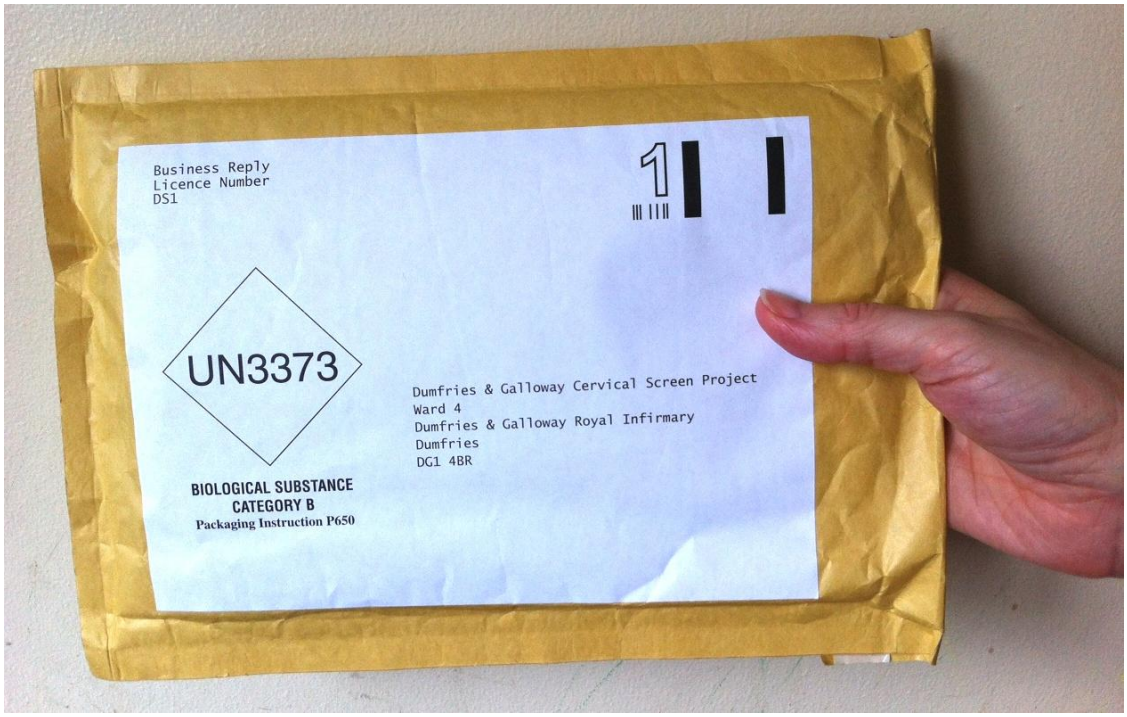


Fig 8.2.14: HPV positive results letter

Ms E….. M……	Sample was collected: 27 Nov 2012
	Reference number: 3006
Date: 10 Dec 2012	Code number: P10- 1645
	CHI number: 0901003242

Dear Madam

Your recent cervical screening test

The cervical screening test that you have had recently has tested positive for Human Papillomavirus (HPV) infection. **This means that further testing is necessary.**

Not all women with HPV infection will have abnormal cells in the cervix. When the HPV infection does not clear up, it can cause damage to the cells in the cervix which could develop into abnormal cells. It is, therefore, **very important that you now have a cervical smear test** in order to rule out the possibility of abnormal cells on the skin of the neck of the womb.

We have arranged this test for you at our 'Smear Clinic' on Ward 4, Dumfries & Galloway Royal Infirmary. Please report to the Reception Area which is on your right as you enter the Ward 4. The Smear Clinic is just in front of the Reception Area.

Appointment: Thursday 13 December 2012 at 12:45

Fig 8.2.15: The negative results letter

Ms D….. J…… Sample was collected: 27 Nov 2012

Reference number: 3007

Date: 10 Dec 2012 Code number: P10- 1646

CHI number: 0901003243

Dear Madam

Your recent cervical screening test

We are pleased to say that your recent cervical screening test for HPV is **negative**. This means that our test did not show any evidence of Human Papillomavirus (HPV) infection in the sample that you self-collected.

Research evidence shows that if a woman does not carry HPV, then the risk of developing cervical cancer is very low indeed. We don't say 'no risk' just 'low risk'. A woman who has ever had sex will probably have come into contact with HPV which might cause cervical cancer, so she should attend regular screening. Therefore, we advise you to accept your next invitation for a cervical smear, which you will receive **anytime within the next 3 years**. A cervical smear test helps to find pre-cancerous cell changes on the cervix whilst the HPV test checks for the virus that can cause these cell changes. If you are tested negative for both HPV and cervical smear, it can give you excellent reassurance.

Regular screening reduces the chance of cancer of the cervix developing. Please remember it is still important to see a doctor as soon as possible anytime you have any unusual discharge or bleeding, including bleeding after sex or between periods.

If you wish to discuss this further, please do not hesitate to contact us. Please find the answers for some frequently asked questions, enclosed. You may wish to visit our study website www.hpvscreening.co.uk for further information.

Appendix 3 (APPROVAL)

Fig 8.3.1: Main ethical approval

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Dr Liliantha Wedisinghe
Specialty Registrar
Dept Obstetrics and Gynaecology
Dumfries and Galloway Royal Infirmary
Bankend Road
Dumfries DG1 4PP

Date 7th June 2011
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Dr Wedisinghe

Study title: **Can women's health be improved by offering more options for cervical screening?**
REC reference: **11/AL/0333**

The Research Ethics Committee reviewed the above application at the meeting held on 02 June 2011. Thank you for attending to discuss the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Discussion

The Committee had several questions which were answered satisfactorily as follows:

1) The Committee noted that this study was a follow on from a previous study and asked you whether there was information available from the new study. You advised that the previous study had shown good results and this has led to this follow up study. You also advised that there had been two much larger studies done in the USA with good results.

2) The Committee asked you to explain how the sample size had been decided. You advised that of the 6,000 non-attendees 30% are expected to respond thus giving an overall sample size of 1,800. Any abnormal results from this sample would automatically link into the standard colposcopy system.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Other Conditions required by the Committee

1) **Participant Information Sheet requires to be amended as follows:**

- Four options are listed for participants to tick the most suitable. There should be a sentence added after Option 4 stating that if this option is selected then participants will be part of a research study.
- There should be a sentence added giving details of the complaints process.
- Contact details should be at the beginning.

2) **The Initial Letter of Invitation requires to be amended as follows**:

- The Committee agreed that the wording of the second sentence in the second paragraph starting 'The majority (70%) of the cervical cancers seen in Dumfries and Galloway etc' was too strong and should either be deleted or reworded.
- Again there should be a sentence added at Option 4 that if this option is selected then they would be part of a research study.
- Contact details should be at the beginning.

3) **Consent Form**

- Contact details should be at the beginning.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		10 May 2011
Investigator CV		03 February 2011
Letter from Sponsor		13 May 2011
Letter of invitation to participant	3 - Initial	07 May 2011
Other: Letter of Invitation - Second	3	07 May 2011
Other: Instructions for use of Medical Device	4	07 May 2011
Participant Consent Form – **to be revised**	3	07 May 2011
Participant Information Sheet – **to be revised**	3	07 May 2011
Protocol	16	07 May 2011
Questionnaire: Non Validated - 1	3	07 May 2011
Questionnaire: Non-Validated - 2	3	07 May 2011
REC application		13 May 2011

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/AL/0333	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Liz Jamieson

Liz Jamieson
Committee Co-ordinator
On behalf of Dr Adam Burnel, Alternate Vice Chair

Enclosures: List of names and professions of members who were present at the meeting
"After ethical review – guidance for researchers"

Copy to: Dr James Lawrence
Dr Gwen Baxter, NHS Dumfries and Galloway

West of Scotland REC 3

Attendance at Committee meeting on 02 June 2011

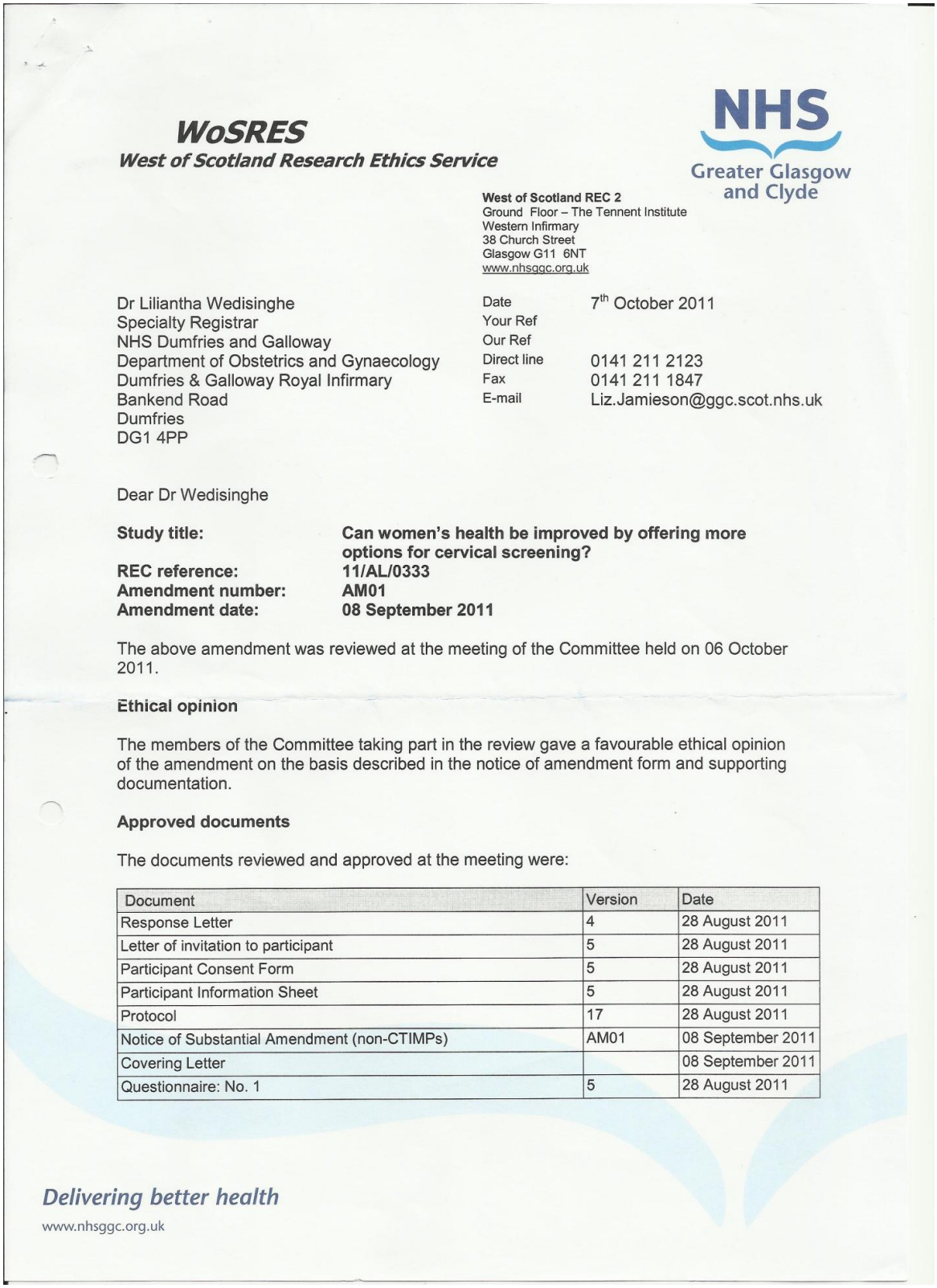
Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Aoisha O'Brien		Yes	
Dr Adam Burnel	Consultant Psychiatrist - Alternate Vice Chair	Yes	
Mrs Bernadette Campbell	Primary Care Support Nurse	Yes	
Dr Paul Fleming	Consultant Clinical Psychologist - Chair	No	
Ms Susan Fleming	Public Health Researcher	Yes	
Ms Isobel Gillespie		Yes	
Mrs Lorna Hammond	Senior Clinical Pharmacist	Yes	
Ms Catriona Kent	Nurse Consultant	No	
Mr Eoin MacGillivray	Lay Member - Vice Chair	No	
Dr Paul Mattison	Consultant Physician in Rehabilitation Medicine	Yes	
Dr Angus McFadyen	Reader in Health Statistics	Yes	
Canon Matt McManus	Lay Member	No	
Dr Stephen Noble	Consultant Anaesthetist	Yes	
Mrs Gillian Notman	Joint Occupational Therapy Lead Advisor	Yes	
Mrs Helen Ross	Lay Member	Yes	
Mrs Rosie Rutherford	Lay Member	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Judith Godden	Scientific Officer/Manager
Mrs Liz Jamieson	Committee Co-ordinator

Fig 8.3.2: Ethical approval- amendment number 1



WoSRES
West of Scotland Research Ethics Service

NHS Greater Glasgow and Clyde

West of Scotland REC 2
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
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Dr Liliantha Wedisinghe
Specialty Registrar
NHS Dumfries and Galloway
Department of Obstetrics and Gynaecology
Dumfries & Galloway Royal Infirmary
Bankend Road
Dumfries
DG1 4PP

Date 7th October 2011
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Dr Wedisinghe

Study title: **Can women's health be improved by offering more options for cervical screening?**
REC reference: **11/AL/0333**
Amendment number: **AM01**
Amendment date: **08 September 2011**

The above amendment was reviewed at the meeting of the Committee held on 06 October 2011.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Response Letter	4	28 August 2011
Letter of invitation to participant	5	28 August 2011
Participant Consent Form	5	28 August 2011
Participant Information Sheet	5	28 August 2011
Protocol	17	28 August 2011
Notice of Substantial Amendment (non-CTIMPs)	AM01	08 September 2011
Covering Letter		08 September 2011
Questionnaire: No. 1	5	28 August 2011

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www.nhsggc.org.uk

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/AL/0333:	Please quote this number on all correspondence

Yours sincerely

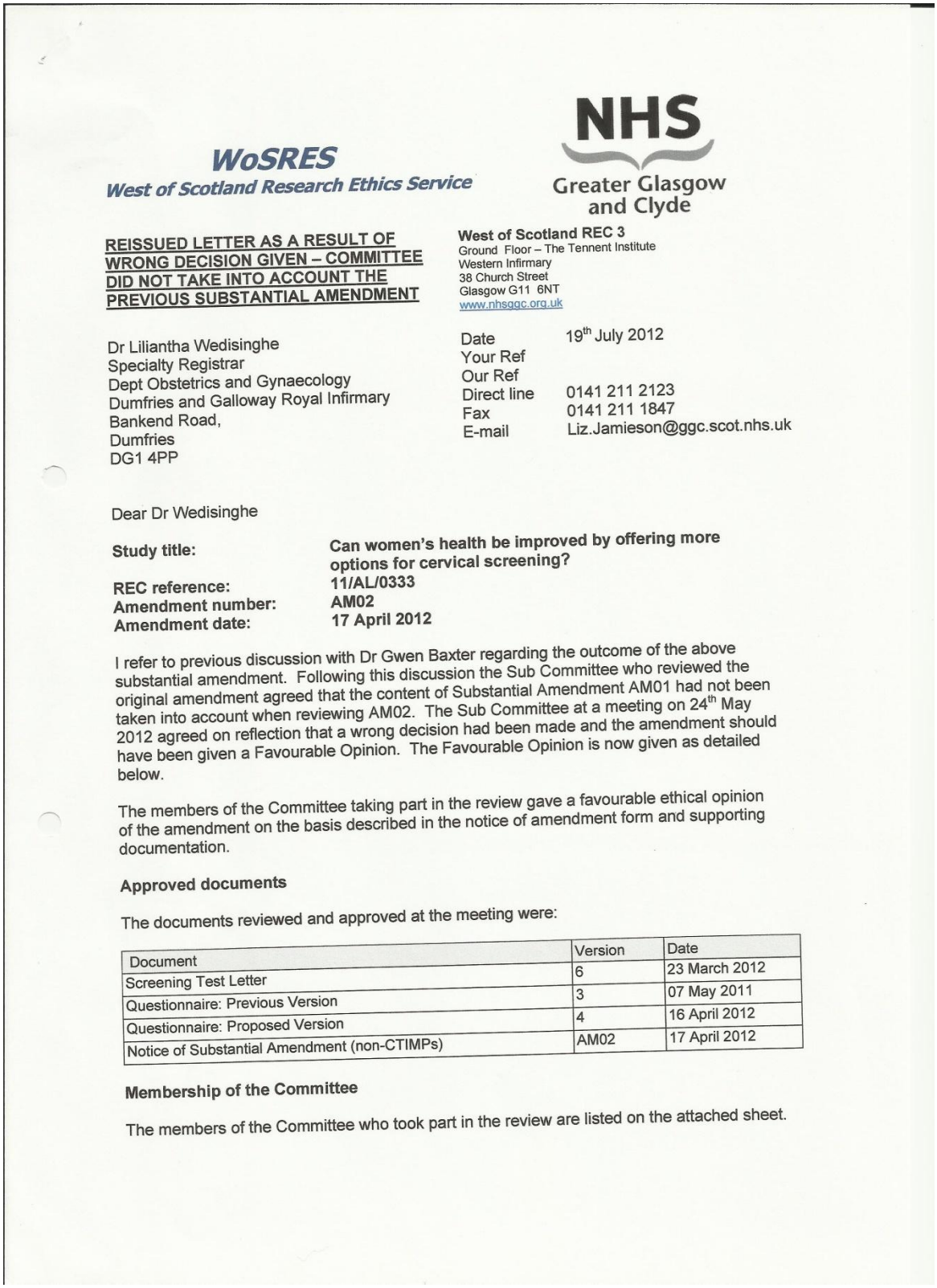
Liz Jamieson

Liz Jamieson
Committee Co-ordinator
On behalf of Dr Adam Burnel, Alternate Vice Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr James Lawrence
Dr Gwen Baxter, NHS Dumfries and Galloway

Fig 8.3.3: Ethical approval- amendment number 2



WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

REISSUED LETTER AS A RESULT OF WRONG DECISION GIVEN – COMMITTEE DID NOT TAKE INTO ACCOUNT THE PREVIOUS SUBSTANTIAL AMENDMENT

West of Scotland REC 3
Ground Floor – The Tennent Institute
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38 Church Street
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www.nhsggc.org.uk

Dr Liliantha Wedisinghe
Specialty Registrar
Dept Obstetrics and Gynaecology
Dumfries and Galloway Royal Infirmary
Bankend Road,
Dumfries
DG1 4PP

Date 19th July 2012
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Dr Wedisinghe

Study title: **Can women's health be improved by offering more options for cervical screening?**
REC reference: **11/AL/0333**
Amendment number: **AM02**
Amendment date: **17 April 2012**

I refer to previous discussion with Dr Gwen Baxter regarding the outcome of the above substantial amendment. Following this discussion the Sub Committee who reviewed the original amendment agreed that the content of Substantial Amendment AM01 had not been taken into account when reviewing AM02. The Sub Committee at a meeting on 24th May 2012 agreed on reflection that a wrong decision had been made and the amendment should have been given a Favourable Opinion. The Favourable Opinion is now given as detailed below.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Screening Test Letter	6	23 March 2012
Questionnaire: Previous Version	3	07 May 2011
Questionnaire: Proposed Version	4	16 April 2012
Notice of Substantial Amendment (non-CTIMPs)	AM02	17 April 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/AL/0333:	Please quote this number on all correspondence

Yours sincerely

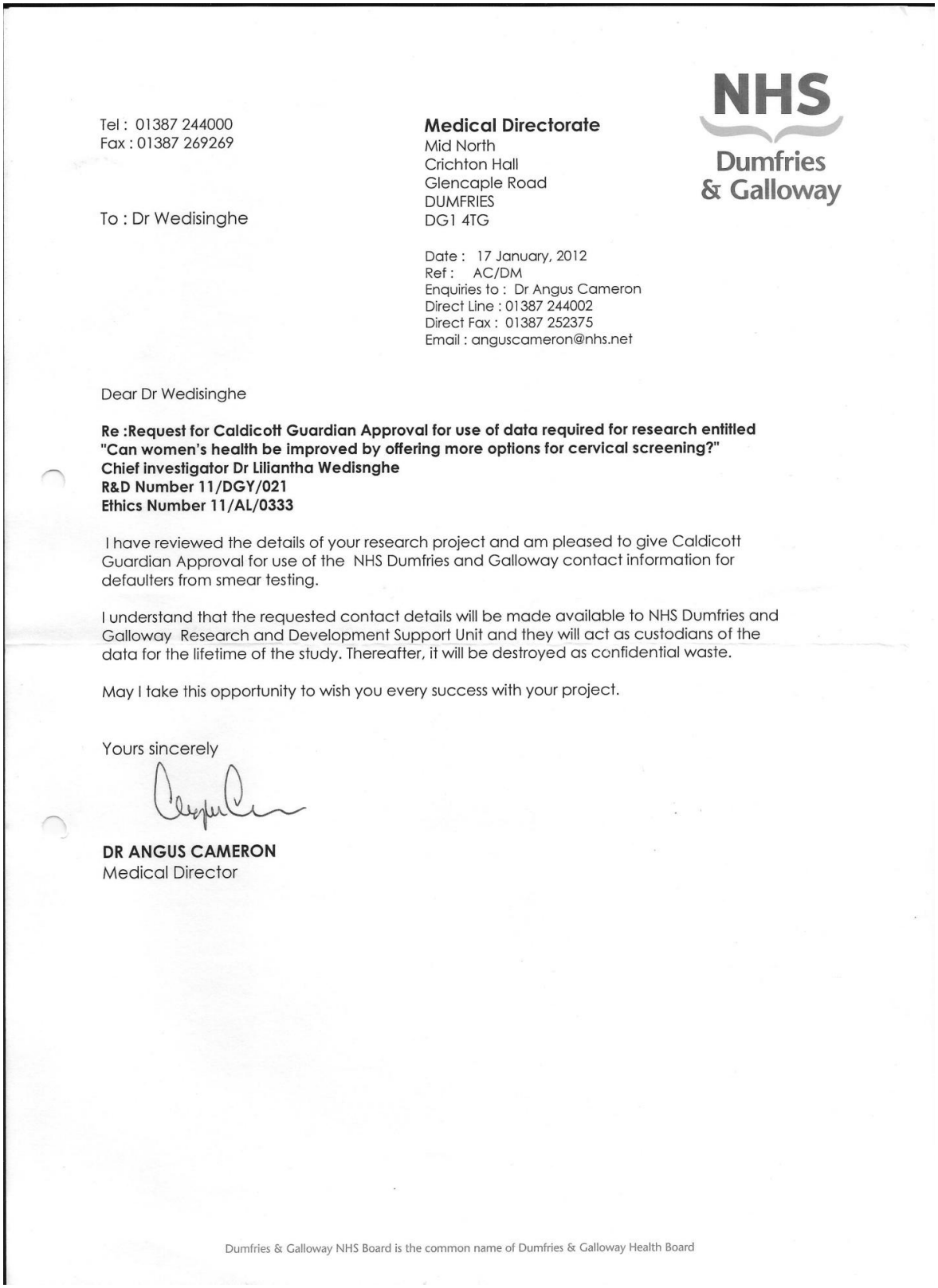
Liz Jamieson

Liz Jamieson
Committee Co-ordinator
On behalf of Eoin MacGillivray, Vice Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Gwen Baxter, NHS Dumfries and Galloway
Dr James Lawrence, NHS Dumfries and Galloway

Fig 8.3.4: Caldecott approval



NHS
Dumfries & Galloway

Tel : 01387 244000
Fax : 01387 269269

To : Dr Wedisinghe

Medical Directorate
Mid North
Crichton Hall
Glencaple Road
DUMFRIES
DG1 4TG

Date : 17 January, 2012
Ref : AC/DM
Enquiries to : Dr Angus Cameron
Direct Line : 01387 244002
Direct Fax : 01387 252375
Email : anguscameron@nhs.net

Dear Dr Wedisinghe

Re :Request for Caldicott Guardian Approval for use of data required for research entitled "Can women's health be improved by offering more options for cervical screening?"
Chief investigator Dr Liliantha Wedisnghe
R&D Number 11/DGY/021
Ethics Number 11/AL/0333

I have reviewed the details of your research project and am pleased to give Caldicott Guardian Approval for use of the NHS Dumfries and Galloway contact information for defaulters from smear testing.

I understand that the requested contact details will be made available to NHS Dumfries and Galloway Research and Development Support Unit and they will act as custodians of the data for the lifetime of the study. Thereafter, it will be destroyed as confidential waste.

May I take this opportunity to wish you every success with your project.

Yours sincerely

DR ANGUS CAMERON
Medical Director

Dumfries & Galloway NHS Board is the common name of Dumfries & Galloway Health Board

Appendix 4 (GLOSSARY OF TERMS) [Edited by PI]

Adenocarcinoma
Cancer arising from glandular tissue (of the cervix). An adenocarcinoma can develop in the glandular lining of the endocervical canal, the narrow passageway that connects the cervix to the womb (inside the canal of the cervix). These cancers are often difficult to diagnose using a cervical smear alone, since the cells inside the canal of the cervix are not as easily collected during the smear test.

Asymptomatic
Not having any symptom of a disease. Many cancers may develop and grow without causing any symptoms, particularly in early stages. Screening tests, for example, a cervical smear test is able to find cervical cancer at the pre-cancer stage of the disease before symptoms start, when the chance of cure is usually highest.

Biopsy
Collection of a sample of tissue that is then examined under a microscope by a Pathologist. This may confirm the presence or absence of abnormal tissue, including cancer. A cervical biopsy taken in a colposcopic examination is considered as the diagnostic test where the disease or the condition is confirmed (or excluded).

Cervix
Neck of the womb. This is the lower, cylindrical end of the womb that connects to the vagina. The part which is exposed to the vagina is called the ectocervix. The central cervical canal is called the endocervix.

Cervical cancer
Cancer of the neck of the womb (uterus). The tumour may spread into surrounding tissue and may involve adjacent organs. It may be detected in a pre-cancerous stage of development by a cervical screening test.

Cervical intraepithelial neoplasia (CIN)
Cellular changes on the surface of the cervix preceding the invasive stages of cervical cancer. The CIN grading system distinguishes three stages, CIN1, CIN2 and CIN3. The three grades of CIN relate to the thickness of the tissue covering the cervix (skin of the cervix) that is affected. CIN 1 means one third of the thickness of the tissue covering the cervix has abnormal cells. CIN 3 means the full thickness of the tissue covering the cervix has abnormal cells. CIN 2 and 3 are collectively termed as high-grade CIN, whereas CIN 1 is called low-grade. All these results mean that they (CIN) are pre-cancerous.

Cervical glandular intraepithelial neoplasia (CGIN)
Cellular changes that occurs in the glandular epithelial cells (lining of the canal of the cervix) preceding the invasive stages of cervical cancer. CGIN is categorised into low and high grade by the Pathologist. Both low-grade CGIN and high-grade CGIN are pre-cancerous

Cervical smear test (also called smear test, liquid based cytology or Pap test)
A test in which a sample collected by a clinician form the neck of the womb that is stained and examined under a microscope. At least 10,000 cells collected from the ectocervix and some cells from the endocervical canal are required for the sample to be deemed adequate for the test

Colposcopy
A procedure in which the lining of the cervix and the vagina are examined using a magnifying telescope (colposcope) for signs of pre-cancerous lesions or cancer (or otherwise).

Coverage (of cervical screening)
The proportion of resident eligible women for cervical screening who have had a cervical screening test with a recorded result at least in the previous 3 years (one screening interval). e.g. the number of women screened divided by the number of resident eligible population.

Defaulters
Eligible women who do not attend following repeat invitations for cervical screening. They are not up-to-date with their cervical smears.

DNA testing
DNA stands for deoxyribose nucleic acid which makes the genetic blue print of organisms. DNA molecules of the Human Papillomavirus (HPV) can be detected using novel technology. This is a very sensitive testing method, and most DNA tests require only a small number of HPV infected cells for an accurate result. Hence, self collected material is more than adequate for this purpose. Research has shown that even a urine sample is also sufficient.

Dyskaryosis
Abnormal cells (of the cervix). The appearance of abnormal cells whose nuclei show the features characteristic of the earliest stage of malignant change. There are 4 categories borderline, mild, moderate and severe. For example, mild dyskaryosis indicates slight cell changes in the cervix, severe dyskaryosis indicates severe cell changes in the cervix. Dyskaryosis can also be categorised into 2 main groups of lesions, low-grade (borderline + mild) and high-grade (moderate + severe). High grade lesions are more likely to develop into cancer, if not treated.

Ectocervical
The outer part of the cervix which is opened into the vagina.

Endocervical
Inside the canal of the cervix.

Eligible women (for cervical screening in Scotland)
Women aged 20 to 60 years who have never had a total hysterectomy.

False negative test result
A test result that appears normal, but in reality is not. There is a potential risk that abnormalities to progressing unknowingly.

False positive test result
A test result that appears abnormal, but in reality is not, thus making additional tests necessary which can cause anxiety.

Glandular abnormality
Abnormality involving the glandular epithelial cells (lining of the canal) of the cervix. Glandular cells appear tall and columnar. They secrete mucous which helps protect the entrance to the womb.

Human Papillomavirus (HPV)
The name for a group of viruses, of which there are more than 100 types

Hysterectomy
An operation in which the womb (uterus) is removed. When the neck of the womb is also removed at the same time, this is referred to as a total or complete hysterectomy. When the cervix is left behind during an abdominal hysterectomy, this is called sub-total. Hence, women who have had a sub-total hysterectomy should have cervical screening tests.

Immodeficiency/ immunosupression
A state in which the ability of the immune system to respond is reduced

Intraepithelial
Within the layer of cells that forms the lining of a part of the body (or a body surface).

Invasive cancer
Cancer that has spread from its original site.

Lesion
Any abnormal tissue or area, usually caused by disease or trauma.

Liquid based cytology (LBC)
It could simply be considered as the medical term for the modern cervical smear test. However, it is a technique for processing cervical screening tests for examination in the laboratory. Immediate transfer of cells into a liquid preservative when the specimen is collected is characteristic of this technique. A sample collected by a clinician form the neck of the womb with a little plastic brush, which gently brushes cells from the neck of the womb. The cells are rinsed directly into a small jar containing 20 millilitres of preservative fluid. This sample is then transported to the laboratory, where it is treated to remove unwanted material. A thin layer of the resulting cell suspension is deposited onto a slide and stained. The slide is then examined under the microscope by the cytopathologist. LBC reduces the rate of unsatisfactory samples and low grade test results, and therefore the need for repeat tests. However, at least 10,000 cells collected from the ectocervix and some cells from the endocervical canal are required for the sample to be deemed adequate for the test.

LLETZ
The acronym for loop electrosurgical excision procedure (Large Loop Excision of

Transformation Zone). A fine wire loop (not too large), through which a safe electrical current flows to generate heat, is used to remove abnormal tissue of the cervix. It often carried out as an outpatient procedure in the colposcopy clinic, under local anaesthesia to numb or freeze the area. The LLETZ treatment is different to the laser treatment.

Neoplasm
A tumour. It is precisely, an abnormal growth that starts from a single altered cell. A neoplasm may be benign (not-cancer) or malignant (cancer). Some benign tumours may be converted into a malignant tumours, over time.

Non-attendees
Eligible women who do not attend following an invitation for cervical screening. Also called defaulters when they failed to respond to repeated screening invitations.

Pathologist/ Cytopathologist
A specialised doctor or health professional who diagnoses disease by studying tissue/ cells under a microscope.

Precancerous
Cells or tissue that is not currently cancerous, but may become so over time.

Referral
The process whereby a patient is transferred from one health professional to another, usually for specialist advice and/or treatment.

Risk factor
Something that increases the chance of developing a disease. In the case of cervical cancer, for instance, a woman with a persistent HPV infection is at greater risk of developing cervical cancer, particularly if her immunity is poor.

Satisfactory smear test
A test that is of sufficient quality for the cytopathologist to issue a valid report.

SCCRS
Scottish Cervical Call-Recall System.

Screening
The search for disease in people who do not have any symptoms. Screening may refer to examination of people with no symptoms, to detect unsuspected disease or condition, such as cancer. The same test used for screening may also be used for the diagnosis. For example, the HPV test is used as a test of cure after the treatment is completed.

Screening test
A means of testing apparently healthy people for presence of a disease or disorder. There are more than seven different screening tests available for Down syndrome screening in pregnancy. Each test has benefits as well as disadvantages. Combined tests are generally more reliable than a

single test. Best suitable screening test/method varies, depending on individual circumstances. Liquid based cytology (LBC) and the HPV test are well recognised screening tests available for cervical screening.

Smear
A cytological preparation made by spreading a specimen (or a part of it) directly onto a glass slide.

Squamous cells
Flat cells that look like scales or plates through a microscope.

Transformation zone
The area (zone) on the cervix where the tall, columnar cell lining of the endocervix undergo changes whilst merging with the squamous cell lining of the ectocervix. This is the area which is most susceptible to the Human Papillomavirus infection. Hence, it is closely examined during colposcopy.

Under screened women
Eligible women who do not regularly attend following an invitation for cervical screening regularly (e.g. every 3 years). Women whose cervical screening test is overdue.

Unscreened women
Eligible women who have never had a cervical screening test.

Unsatisfactory smear test
A cervical screening test which cannot be properly assessed microscopically due to poor quality or too few cells (less than 10,000 squamous cells and/or no endocervical cells). A repeat test is advised.

Uptake rate (of cervical screening)
The proportion of women invited to a cervical screening appointment who actually attend.